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PATHOLOGIC ASPECTS OF ACUTE EPIDEMIC HEPATITIS, WITH ESPECIAL REFERENCE TO EARLY STAGES

Report of a Series of Ten Cases, Including a Case in Which There Was Spontaneous Rupture of the Spleen and Six Cases of Fulminating Disease in Patients Who Had Been Wounded Several Months Previously

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EPIDEMIC hepatitis is a disease which has long been of importance in military medicine and which, as a result, receives the greatest attention in time of war. There is considerable confusion in regard to the etiologic agents and the nomenclature of the disease. It has been and is known by a variety of names—"epidemic catarrhal jaundice," "campaign jaundice," "acute catarrhal epidemic hepatitis," "infectious hepatitis," "acute infective jaundice" and "infective jaundice." "Homologous serum jaundice" is a term applied to a type of jaundice which develops occasionally as a sequel to the transfusion of plasma or whole blood or to the inoculation of biologic products containing human serum. The etiologic agents in epidemic hepatitis and homologous serum jaundice appear to be quite similar and may even be identical. None of the various synonyms just cited is especially satisfactory. Current usage here and abroad favors the term "epidemic hepatitis." Even though epidemic hepatitis and homologous serum jaundice may be caused by the same agent or by agents which differ only slightly antigenically, it may be well for the time being to continue the use of the two terms, to emphasize not only the difference in route of infection but differences in period of incubation and in severity of clinical course.

In peacetime, as a rule, only isolated cases are encountered, although periodically there have occurred scattered epidemics among civilians. The isolated or sporadic cases have been referred to as endemic

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hepatitis. Most authorities are of the opinion that endemic and epidemic hepatitis are one and the same disease, although the matter is still controversial. Conditions occasioned by campaigns, and possibly transfusions of whole blood or plasma containing the icterogenic agent in the field, give rise to factors which are favorable for outbreaks of the disease.

Recent experiments have shown definitely that the disease is due to a filter-passing agent, probably a virus. Havens,[1] also Neefe and co-workers,[2] as well as others,[3] have recently produced hepatitis in human volunteers by a number of methods. Their experiments emphasize three important features: (*a*) The "virus" is in the feces; (*b*) the disease can be produced by feeding either serum, feces or nasal washings to human subjects; (*c*) inoculation of comparable material usually gives rise to a longer period of incubation than does feeding.

The striking difference in incubation period, depending on whether the virus is inoculated or enters by way of the alimentary tract, is one of the unexplained peculiarities of the disease. According to Paul,[4] in the former case the period of incubation varies from fourteen to one hundred and sixty days, with a general range of sixty to one hundred and twenty days, in contrast to a period of from twenty to forty days in the latter case. In the latter instance the incubation period conforms more closely to that observed clinically. There are occasional cases, however, in which there is no history of known contact but in which a transfusion of blood or plasma has been given two to three months previously. Various studies of the 1942 outbreak in the Army of the United States following the use of yellow fever vaccine suggest clearly that the hepatitis (homologous serum jaundice) which has been produced in such cases was due not to the yellow fever virus in the vaccine but to the virus of epidemic hepatitis. At that time human serum was used in preparation of yellow fever vaccine.[5] Observations made following administration of icterogenic material to human volunteers conformed closely to clinical observations. For example, Neefe and co-workers[2] showed that a much longer period of incubation ensued when the icterogenic material was intro-

1. Havens, W. P., Jr.: Experimental Production of Infectious Hepatitis by Feeding Icterogenic Materials, in Conference on Liver Injury, Sept. 18-19, 1944, New York, Josiah Macy, Jr. Foundation, 1944, pp. 78-80.

2. Neefe, J. R.; Stokes, J., Jr.; Rienhold, J. G., and Lukens, F. D. W.: J. Clin. Investigation **23**:836, 1944.

3. Findlay, G. M., and Martin, N. M.: Lancet **1**:678, 1943.

4. Paul, J. R.: Hepatitis: Clinical and Epidemiological Aspects, in Conference on Liver Injury, Sept. 18-19, 1944, Josiah Macy, Jr. Foundation, 1944, pp. 75-77.

5. Turner, R. H.; Snavely, J. R.; Grosman, E. B.; Buchanan, R. N., and Foster, S. O.: Ann. Int. Med. **20**:193, 1944.

duced intravenously than when it was introduced into the alimentary tract. Quite uniformly in clinical cases of homologous serum jaundice following yellow fever vaccination long incubation periods have been recorded similar to those observed in human volunteers. In the army outbreak of 1942 it was observed that the interval between the date of yellow fever vaccination and the onset of the disease varied from forty to one hundred and twenty days, with the onset occurring as much as six months later in a few cases. In the Navy, DeVeer and Matzner [6] reported a fatal case of yellow fever vaccination in which the onset of symptoms occurred four months after the transfusion of blood or plasma. Beeson [7] reported 7 cases of jaundice occurring one to four months after transfusion of blood or plasma. Intervals of seventy-eight to eighty-three days were noted by Propert [8] in 7 children who had received inoculums from the same batch of measles convalescent serum. Three of the children died and showed the lesions of "acute yellow atrophy." Findlay and Martin [3] transmitted the disease to human volunteers by transferring nasal washings from patients with jaundice due to fever vaccine. They accomplished the transmission by intradermal instillation and noted incubation periods of twenty-eight, thirty and fifty days. Voegt [9] observed jaundice four weeks after oral ingestion of duodenal juice. The incubation period for acute epidemic hepatitis is variously stated, but the following figures are representative: twenty to forty days (Paul [4]), twenty to thirty-one days (Newman [10]), twenty-six to thirty-five days (Pickles [11]) and fourteen to thirty-seven days (Ford [12]).

The manner in which epidemic hepatitis spreads is unknown. Neefe [2] in the light of experiments already cited is of the opinion that it is spread by droplet infection directly, by fomites indirectly. In a study of a recent civilian epidemic at a boys' and girls' camp in Pennsylvania Neefe and Stokes [13] demonstrated evidence which indicated that the icterogenic agent was water borne, the epidemic being secondary to fecal contamination of well water. In this study they failed to demonstrate the presence of the causative agent in either the nasal washings or the urine of 26 and 38 patients, respectively. In epidemics, several modes of transmission may be concerned. Of epidemiologic importance is the peculiar seasonal incidence—a sharp rise in the autumn months and an equally sharp drop in winter.

6. DeVeer, J. A., and Matzner, M. J.: U. S. Nav. M. Bull. **42**:1381, 1944.
7. Beeson, P. B.: J. A. M. A. **121**:1332, 1943.
8. Propert, S. A.: Brit. M. J. **2**:677, 1938.
9. Voegt, H.: München. med. Wchnschr. **89**:76, 1942.
10. Newman, J. L.: Brit. M. J. **1**:61, 1942.
11. Pickles, W. N.: Brit. M. J. **1**:944, 1930.
12. Ford, J. C.: Lancet **1**:675, 1943.
13. Neefe, J. R., and Stokes, J.: J. A. M. A. **128**:1063, 1945.

Fortunately, the disease is usually mild, with a low mortality rate. In the different localities and different armies in which epidemics have occurred, this rate has varied from 0.13 to 0.44 per cent.[14a] As a result of the low mortality, there has not been until recently much opportunity to study thoroughly the morphologic aspects of the disease.

From the standpoint of morphologic anatomy, knowledge of epidemic hepatitis has been rather meager, especially that pertaining to cases in which the disease is fatal in the early stages and to those cases in which acute "homologous serum jaundice" occurring in previously wounded men is fatal a few days after the onset of jaundice. Inasmuch as most of the data referable to the morphologic anatomy of this disease have been obtained from cases in which the infection has run a protracted course, little is known about the incipient and early changes, some of which may later disappear or subsequently become secondarily altered or completely obscured. It is well recognized that the principal lesions are found in the liver, although associated lesions have been described—principally those of the spleen and the regional lymph nodes. Descriptions of hepatic, splenic and lymph node lesions have almost uniformly been limited to those cases in which the disease ran a course varying from ten days to four months, with an average of one to two months. In 8 of the 10 cases to be reported in this paper, the clinical course varied from two to ten days. As will be discussed later, it is suspected that in at least 5 and probably 6 of these cases the icterogenic agent was introduced in plasma or whole blood transfusions, and that these cases might well be classified as instances of "homologous serum jaundice." In these cases not only characteristic lesions were seen but other early lesions, hitherto undescribed. Some of the latter were probably transient, as the presence of such lesions had not been previously noted or emphasized in the more protracted clinical cases.

Essentially the hepatic lesion as recognized at the present time is one of irregular distribution which involves the hepatic cells (hepatocellular necrosis) without damaging the sinusoids or the reticular framework. Destruction (autolysis) of the damaged liver cells is thought to occur rapidly. Because of the irregular involvement, large areas of parenchyma may be destroyed while elsewhere there is no destruction or it is incomplete. Limitation of the destructive process to the liver cells with preservation of lobular outlines (due to nondestruction of sinusoids and reticular framework) is thought to be highly characteristic of epidemic hepatitis. In the earlier phases the stroma is variably infiltrated by inflammatory cells (lymphocytes, mononuclear phagocytes and leukocytes in varying proportions). Even so,

14. Lucke, B.: (*a*) Am. J. Path. **20**:471 and (*b*) 595, 1944.

no scarring occurs—merely condensation of preexistent stroma. The destructive process initially involves those liver cells situated about the central lobular venules. Later it may progress so as to involve either part or all of the lobule. Frequently the central lobular venules show endophlebitis, which is most conspicuous in the earlier stages of the disease. Inclusion bodies such as are frequently observed in other virus diseases have not been described in epidemic hepatitis. In many respects the lesion of the liver resembles that of idiopathic acute yellow atrophy. Most recent writers [15] on the subject are of the opinion that the hepatic lesion in the fatal case of epidemic hepatitis may be and usually is indistinguishable from so-called idiopathic yellow atrophy. In fact, in those cases of "acute yellow atrophy" in which a known cause can be excluded (i. e., chloroform, carbon tetrachloride, cinchophen, mushroom toxins, phosphorus, arsenic and bacterial toxins) it is probable that the essential disease is epidemic hepatitis. In other words, when a pathologist discovers "idiopathic acute yellow atrophy" at autopsy, the burden of proof is on him to exclude the probability of epidemic hepatitis. In such cases, concurrent lesions in other organs, such as meningoencephalitis, acute regional lymphadenitis, orchitis or acute splenitis, may be of considerable assistance in establishing the diagnosis. The damaged areas are repaired by regeneration (hyperplasia), from residual liver cells located peripherally in the lobules and possibly from the small perilobular (septal) bile ducts, which begins early. In the fatal cases the restitution of normal lobulation (architectural pattern) is seldom perfect, although in cases in which clinical recovery has occurred the anatomic repair is such as to approach closely normal structure, often with no residual changes being evident. Lucke in two recent articles has contributed much to the former meager pathologic knowledge of this disease. In one article [14a] he analyzed the morphologic material obtained by the Army Medical Museum in 125 fatal cases of the outbreak of jaundice which occurred in the Army of the United States during the spring and summer of 1942. The mortality rate in this outbreak was 0.24 per cent. In the second paper [14b] he described the hepatic lesions in 14 people who had recovered from epidemic hepatitis but who died at intervals varying from one week to fourteen months later either of unrelated disease or as the result of an accident. Dibble, McMichael and Sherlock [15a] by aspiration biopsy obtained valuable data referable to hepatic lesions during different stages of the disease in 56 cases.

According to published reports, the mortality from epidemic hepatitis in the United States Navy has been practically nil. Fortu-

15. (*a*) Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Lancet **2**:402, 1943. (*b*) Cockayne, E. A.: Quart. J. Med. **6**:1, 1912-1913. (*c*) Lucke.[14a]

nately, in contrast to the army experience of 1942, little "contaminated" yellow fever vaccine, made with human serum, was released to the navy. During the past two years, however, several outbreaks of epidemic hepatitis have occurred at various naval establishments at home and abroad. Willard [16] reported an epidemic occurring at a base hospital with "more than 750 admissions." An outbreak of 320 cases at an unidentified United States naval hospital was reported by Simpson, Powers and Lehman.[17] Logan [18] reported 45 cases from the United States naval hospital in Philadelphia. Cohen [19] at an advance United States naval base hospital reported 360 cases. An outbreak of 73 cases in Tunisia was investigated by Gezon.[20] The fact that in all these epidemics no deaths occurred emphasizes not only the low mortality of the disease but the scant opportunity pathologists have had to study it from the point of view of pathologic anatomy. A group of 30 cases was reported by DeVeer and Matzner,[6] in all but 1 of which recovery occurred. The exception was a case of post-vaccinal (yellow fever) jaundice. The incubation period in this case was approximately four months, and the characteristic lesions of the liver were indistinguishable from those of epidemic hepatitis.

MATERIAL

Inasmuch as present anatomic and histologic knowledge of epidemic hepatitis is still rather meager, and in view of the extremely few deaths from this cause reported in the naval service, the addition of a report of other cases, especially of those with unusual features, to the literature seems warranted at this time.

During the past twenty-one months at two naval hospitals in the San Francisco Bay area the author has had the unusual opportunity of making autopsies on 10 persons who died of this disease—all white personnel. Three were encountered at one institution and 7 at another. Although there were a number of patients with "catarrhal jaundice" at each institution their number was not as great as one would have expected from the number of deaths, considering the low mortality rates which have been reported elsewhere to date. This may be due in part, however, to several factors. First, in both hospitals many of the patients were received from ships afloat and from installations overseas, and, second, a number of the patients with the disease had been previously wounded, had received multiple transfusions and had probably suffered considerable loss of nitrogen consequent to their wounds. These men had been wounded three to three and one-half months previously. In this group of wounded men who subsequently contracted hepatitis, the disease seemed to be much more virulent and associated with a higher mortality rate than has been generally observed heretofore. In a group of 32 wounded men in whom jaundice later developed there were 6 deaths, or a mortality of 19 per cent.

16. Willard, J. H. W.: U. S. Nav. M. Bull. **42**:1085, 1944.

17. Simpson, W. M.; Powers, W. L., and Lehman, R. G.: U. S. Nav. M. Bull. **41**:1620, 1943.

18. Logan, V. W.: U. S. Nav. M. Bull. **43**:271, 1944.

19. Cohen, M. I.: U. S. Nav. M. Bull. **43**:1166, 1944.

20. Gezon, H. M.: U. S. Nav. M. Bull. **43**:579, 1944.

These men most probably had "homologous serum jaundice," although proof is lacking.

In view of the facts that in most of the cases in the total series of 10 (see table) death occurred in the early stages of the disease, considerably earlier than heretofore reported in the literature, the mortality was unprecedented, and because a number of the patients probably had "homologous serum jaundice," a rather detailed description of the clinical, anatomic and histologic findings will be presented.

In addition to the classic hepatic changes which were shown in all the cases, there were other features of interest. Nervous and mental manifestations dominated

Summary of Data on Cases in Which Death Was Due to Acute Hepatitis

Case	Age, Yr.	Duration of Hepatitis (Clinical), Days	Neurologic Disturbances	Size of Liver, Gm.	Ascites, Cc.	Size of Spleen, Gm.	Complications	Maximal Interval of Time for Possible Transmission by Transfusion, Months
1	21	7	++++	850	0	211	Wounds, multiple, old (?)	3½
2	24	4	++++	1,000	0	...	Pachymeningitis	4
3	27	2 (?)	..	1,912	?	622	Hemoperitoneum	
4	22	9	++	1,125	0	258	Wounds, multiple, old	3
5*	24	7	++	?	0	?	Wounds, multiple, old	3
6	23	10	++	1,135	50	325	Wounds, multiple, old	3
7	23	6	+	1,475	0	400	Wounds, multiple, old	3½
8	19	6	..	1,727	300	517	Wounds, multiple, old	4
9	28	62 (?)	..	860	1,000	260	Bacterial endocarditis	
10	23	47 (?)	..	1,800	4,600	585	Recovery with recurrence	

* No autopsy was made. Liver tissue was obtained for biopsy with a Vim-Silverman needle.

the clinical picture in 2 cases. Spontaneous rupture of the splenic capsule with fatal hemoperitoneum occurred in another case on the second day of clinical illness. Six patients had sustained battle wounds three to four months previously. To the best of my knowledge the previously wounded men had not been in contact with persons who had hepatitis. Anatomic material was obtained by autopsy in 9 cases and by biopsy of the liver with a Vim-Silverman needle in another. The initial symptom in 2 cases was abdominal distress which was of such constancy and nature as to render both patients candidates for laparotomy.

CASES IN WHICH NERVOUS AND MENTAL MANIFESTATIONS PREDOMINATED

CASE 1.—The patient was a private in the United States Marine Corps, 21 years old. The duration of his hepatitis was seven days. He complained of nausea and vomiting.

The patient had received multiple shrapnel wounds four and one-half months previously, June 27, 1944, while in combat on Saipan. Among these wounds was a compound fracture of the left femur. He was hospitalized, but records of that hospitalization are not available. It seems probable, however, in view of the severity of his wounds, that he must have received transfusions of whole blood or plasma or both. By November 1 he was ambulatory and able to bear his full weight on the injured leg. Three weeks prior to the terminal episode he had an attack of nausea and vomiting, from which he had apparently recovered. The evening of November 17 he became nauseated and vomited.

The results of his physical examination were essentially negative. His temperature, pulse and respirations were normal. The skin and the scleras revealed no abnormal changes of color. There was no abdominal tenderness. Neurologic findings were uniformly negative.

The nausea and vomiting continued at intervals with no accompanying symptoms for four days. During this four day period there were several stools, all of which appeared normal. Early in the afternoon of November 21 he showed transitory improvement and was able to retain liquids. In the evening, however, he became restless and rather irrational. His temperature, pulse and respirations were still normal. The next morning (November 22) the patient was alternately delirious and comatose. Physical findings, as well as the results of examinations of blood and urine, remained essentially negative. In the afternoon there were noted a positive Babinski reflex, generalized hyperactivity of the knee reflexes and absence of superficial reflexes. The fundi were normal, and there was no nuchal rigidity. Spinal fluid findings were all within normal limits except for a slight elevation of the sugar. A sample of blood taken November 22 showed a carbon dioxide-combining power of 37 volumes per cent. Beginning at 5 a. m., November 23, convulsions occurred at intervals, and the patient became feverish. He was hyperventilating to a marked degree. For the first time it was noticed that he was markedly jaundiced. At 9 a. m. he was still hyperpneic, with waves of decerebrate rigidity occurring every five minutes. Rectally the temperature had risen to 107.6 F. Palpation revealed no enlargement of the liver. The blood carbon dioxide-combining power had dropped to 24 volumes per cent and the blood sugar to 70 mg. per hundred cubic centimeters. Therapy consisted of intravenous injections of dextrose, calcium gluconate, nicotinic acid and vitamin B complex. His temperature dropped to 104 F. in the afternoon, and his respirations became nearly normal, although waves of decerebrate rigidity continued to occur. The patient died at 4:20 a. m. November 24.

The clinical diagnosis was cerebrovascular accident (cause in question).

Pathologic Observations.—The skin, the scleras, the mucous membranes and the conjunctivas showed a moderate chrome icterus.

The liver was markedly shrunken and weighed 850 Gm. Glisson's capsule was diffusely wrinkled. On cut section the parenchyma was flabby and brownish red, with a loss of lobular markings except for the lateral portion of the left lobe. Here lobular markings persisted. Histologic sections from different areas showed changes typical of so-called idiopathic acute yellow atrophy. Most of the liver cells were absent. Lobular outlines persisted, however, the portal triads being preserved but situated closer to one another than in the normal liver. In subtotally destroyed lobules the autolysis of liver cells involved the central and midzonal areas of the lobules; only the peripheral hepatic cells remained. The sinusoids in the damaged areas were closely approximated, widely dilated and engorged with blood. Small groups of lymphocytes infiltrated the walls of the central venules and focally infiltrated the stroma elsewhere. Fat stains of frozen sections revealed only scant lipoid.

The spleen was slightly enlarged and weighed 211 Gm. Its pulp was firm and dark reddish brown.

Both kidneys were slightly swollen and possessed pale yellowish orange cortices. The left kidney weighed 195 Gm. and the right 187 Gm. Histologic sections revealed extensive fatty phanerosis of the epithelium of the convoluted tubules.

The regional lymph nodes were moderately enlarged and spongy. Microscopically, they were diffusely infiltrated by an admixture of lymphocytes and poly-

morphonuclear leukocytes. Some of their germinal centers were large and edematous and were infiltrated by occasional polymorphonuclear leukocytes.

Sections of the pyloric and fundic portions of the stomach revealed no significant changes. The testes were not examined.

The brain weighed 1,525 Gm. There was considerable congestion of the leptomeninges, which was most marked over the left temporal and occipital regions. A few tiny hemorrhages occurred beneath the ependymal lining of the fourth ventricle. A few tiny petechial spots with variable peripheral discoloration occurred in the mesencephalon rostral to the pons. Several tiny foci of slight softening were detected in the region of the substantia nigra at the level of the mamillary bodies. Histologic sections revealed a few tiny perivascular hemorrhages in the mesencephalon, a slight perivascular lymphocytic infiltration in the tegmentum of the pons and mild meningoencephalitis, which was most evident about the brain stem and the cerebellum. No significant changes were noted in the ganglion cells.

The anatomic diagnosis was: acute epidemic hepatitis with jaundice; mild meningoencephalitis; multiple tiny hemorrhages of the midbrain.

Case 2.—A chief quartermaster of the United States Navy, 24 years old, had hepatitis for approximately four days. His complaint was pain in the epigastrium, lasting one day.

His past history was as follows: July 5, 1943 he sustained immersion blast injuries after having abandoned ship. While he swam and until he was rescued, four hours later, he suffered much abdominal pain. After his rescue the results of his physical examination were negative except for mild distention and tenderness of the abdomen, which also showed slight generalized rigidity. On July 5 he was given 500 cc. of plasma intravenously. By July 18 the abdominal soreness had disappeared. His recovery was uneventful and he was returned to duty July 21.

Oct. 24, 1943 he reported to the sick bay aboard his ship. He stated that he had experienced slight pain in the "stomach" for one day, and that on the preceding day he felt slightly ill and had a chill, at which time he felt feverish. His temperature, pulse and respirations were normal. He became somewhat nervous, and slight irritation of the throat developed. By the evening of the next day he had become gradually semicomatose and could be aroused only with difficulty. Incontinence developed, and stupor deepened. The pupils were equal but dilated. All the reflexes were normal. October 27 he was transferred to a United States naval hospital. At this time he was comatose and could not be aroused.

His temperature was 101.4 F.; pulse rate, 150; respirations, 40 per minute; blood pressure, 155 systolic and 75 diastolic. He was comatose and appeared critically ill. The skin and the scleras were moderately jaundiced. The pupils were equal and reacted to light. There was mild opisthotonos. Occasionally there occurred convulsive tremors, which were predominantly right sided. The knee jerks were extremely hyperactive. Ankle clonus was marked. Abdominal reflexes and nuchal rigidity were absent. His breathing was stertorous.

On his admission to the hospital at 12:05 a. m. October 27, the spinal fluid was clear and was under a pressure of 150 mm. of water. There were 3 white blood cells per cubic millimeter. The Pandy test was negative. Spinal fluid from a second lumbar puncture nine hours later was xanthochromic. It contained 12 white blood cells and 660 red blood corpuscles per cubic millimeter. The white cell count of the blood was 14,000, with 17 per cent polymorphonuclear leukocytes. A blood smear was negative for plasmodia. Mild right-sided convulsive seizures developed. The patient succumbed thirteen hours after he entered the hospital.

The clinical diagnosis was acute encephalitis.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed moderate icterus. The liver was markedly shrunken and weighed 1,000 Gm. Glisson's capsule was wrinkled, especially over the left lobe. On cut section the parenchyma was found to be flabby, brownish red and slightly edematous. Lobular markings were indistinct. Water-clear bile was contained in the bile ducts. Over the right lobe of the liver anteriorly was a broad depressed scar with a few fibrous adhesions between it and the anterior abdominal wall. Histologically, extensive hepatocellular necrosis and autolysis of liver cells were observed.

Peripherally in a few scattered lobules occasional liver cells remained. The sinusoids appeared widely dilated, closely grouped and engorged with blood. Small groups of lymphocytes were focally distributed throughout. Fat stains of frozen sections revealed no lipoid.

The right kidney possessed a rather broad, slightly depressed scar anteromedially, over which the capsule was adherent.

Fibrous adhesions occurred between several loops of ileum and occurred elsewhere in the peritoneal cavity. Multiple purpuric hemorrhages occurred beneath the peritoneum, the pericardium, the endocardium and the mucosal lining of the renal pelves.

The dura mater showed an area of internal hemorrhagic pachymeningitis over the right parietal lobe with adhesions to an area of the leptomeninges overlying a cortical scar. Histologic sections showed slight fibrous thickening of the dura with occasional presence of pigment-laden phagocytes. Covering the inner aspects of the dura was much recent hemorrhage. The brain showed a rather broad depressed scar in the right parietal lobe immediately beneath the area of pachymeningitis. Histologic sections through this area showed considerable loss of cortical tissue. Microglial cells were increased in number, and there were occasional multinuclear phagocytes laden with brown granular pigment.

The anatomic diagnosis was as follows: acute epidemic hepatitis; ecchymotic hemorrhage of the peritoneum, the pericardium, the endocardium and the renal pelvis; subdural hemorrhage; internal hemorrhagic pachymeningitis; dural-leptomeningeal adhesions; cerebral cortical scar; scars of the liver and the right kidney.

The neurologic signs noted clinically in case 1 cannot be ascribed to any one specific lesion. The demonstrable brain changes were characterized by mild meningoencephalitis and a few tiny hemorrhages occurring in the mesencephalon and in the floor of the fourth ventricle. It seems most probable that the nervous and mental manifestations were on a physiologic rather than an anatomic basis. Characteristically the liver showed lesions typical of acute epidemic hepatitis. In the second case the neurologic disturbances were secondary to a coincidental finding of great interest. It seems probable that this man's prothrombin level had been lowered as a result of the extensive hepatic damage, making conditions favorable for an exacerbation of bleeding from the area of pachymeningitis. The pachymeningitis arising in the absence of the usual predisposing factors (tuberculosis, syphilis and alcoholism) is of extreme interest in view of the immersion blast injury which had been sustained four months previously. The adhesions between the area of pachymeningitis and the underlying scarred cerebral cortex suggest a sudden contusion as the most probable etiologic factor.

The dural and cerebral scars associated with the scars in the right lobe of the liver and the multiple peritoneal adhesions suggest most strongly that the submersion blast injury sustained four months previously had been the common causative factor. Dural and cerebral cortical lesions secondary to immersion blast injuries have not been previously described.

EARLY ACUTE HEPATITIS COMPLICATED BY SPONTANEOUS RUPTURE OF THE SPLEEN AND FATAL HEMOPERITONEUM

In the past there has been little opportunity to study the liver, the spleen and other tissues during the early stages of acute epidemic hepatitis. In the army series of 125 cases [14a] the patient showing the earliest stage at autopsy had survived ten days. In this regard Lucke stated: "None of the livers in this series were in the early stages of destruction; indeed so far as I have been able to learn from the literature, no one has ever seen the earliest stage in this disease, which rarely terminates in its most acute stages." Not only has knowledge of the early stages of the hepatic changes been scanty but especially information pertaining to early changes in the spleen and other organs. Most of the data available on early hepatic changes have been obtained by aspiration biopsy.[15a] Few patients with this disease die in the preicteric and intermediate phases. For this reason there is little available knowledge referable to the state of the spleen as well as of other organs in the initial stages of the disease. According to the scant data now in the literature, the spleen is soft for a short while in the early stages of involvement. Later, however, it is uniformly firm and usually enlarged to a moderate degree. In the case to be reported the clinical duration of hepatitis is estimated to have been not more than two days. The spleen was enlarged and extremely soft. A tiny laceration of the splenic capsule overlying a subcapsular hemorrhage resulted in a fatal hemoperitoneum. Unfortunately, it was not possible to obtain data on the prothrombin level in this case. It seems probable in view of the histologic observations, however, that splenitis, rather than a low level of prothrombin, was an important factor in initiating the subcapsular hemorrhage. The acute interstitial pneumonitis, myocarditis and orchitis concurrent with the splenitis and the hepatitis are indicative of a virus origin.

CASE 3.—The patient was a pharmacist's mate 27 years old. The duration of the hepatitis was estimated to have been not over two days. The complaint was fatigue for possibly two days, with jaundice developing in one day.

The patient had never been outside of the United States and had had no serious illnesses. Four weeks prior to the hepatitis he had an acute febrile illness which was characterized by a morbilliform eruption and posterior cervical lymphadenopathy. This illness was diagnosed as "German measles." He was hospi-

talized one week and was returned to duty around November 20. On December 4 he departed with a draft of patients to Great Lakes, Ill. En route, a fellow corpsman became ill, jaundice developed, and the man had to be removed from the train to a hospital in Chicago. This man died a few days later and the necropsy was reported as showing "idiopathic acute yellow atrophy of the liver." On the return trip by train the pharmacist's mate complained of fatigue and on the last day of the journey noticed slight jaundice. He became progressively weaker, and an ambulance was ordered to meet the train. The patient died in the ambulance December 16 while en route to the hospital.

Pathologic Observations.—The skin and the scleras were pale lemon yellow. The peritoneal cavity contained 2800 cc. of fluid blood.

The liver was slightly enlarged and weighed 1,912 Gm. Glisson's capsule was smooth and pale chocolate brown, and the edges of the liver were slightly rounded. The hepatic parenchyma was slightly opaque, yellowish orange and ischemic, and its lobular markings were indistinct. Histologic sections revealed extensive stromal and parenchymatous changes. Many of the liver cells were swollen, and all were detached from one another in varying degrees, frequently disrupting the continuity of the hepatic cell cords (fig. 1*A*). Even though these changes were diffuse, they seemed more accentuated in the central and midzonal portions of the hepatic lobules. Not infrequently the biliary canaliculi were slightly dilated and contained yellowish brown bile. Infiltrating the stroma were prominent groups of lymphocytes and mononuclear phagocytes. Fat stains of frozen sections revealed a scant amount of lipoid. Some of the swollen hepatic cells contained large vacuolated oval nuclei. No inclusion bodies were seen.

The spleen was greatly enlarged, soft and flabby. It weighed 622 Gm. and measured 21.5 by 12 by 3.5 cm. Medially along the convexity of the lower third the capsule was lacerated over an area measuring 1.5 by 2 cm. Immediately beneath and about the laceration was a large subcapsular hemorrhage which measured 8 by 10 cm. Otherwise, the capsule was smooth and grayish purple. The pulp was semiliquid, pale grayish brown and quite opaque. Histologically, the malpighian bodies were small, compact and discrete. The pulp was extremely cellular, being infiltrated by a myriad of lymphocytes. Prominent areas of edema occurred in places (fig. 2*A*).

The testes were grossly normal but histologically showed moderate to marked arrest of spermatogenesis. Infiltrating the testicular stroma were a few widely scattered small groups of lymphocytes (fig. 2*B*).

The heart microscopically showed myocarditis. Small groups of lymphocytes with occasional mononuclear phagocytes infiltrated the myocardium between the muscle fibers of the trabeculae carneae and also were prominent immediately beneath the endocardium.

The lungs were firm but aerated throughout. Histologically, the pulmonary alveolar walls were moderately thickened because of edema and moderate numbers of infiltrating lymphocytes and mononuclear phagocytes. Similar cells also formed moderate perivascular collars. Most of the alveoli were empty except for a few pigment-laden phagocytes.

The regional lymph nodes, mainly the mesenteric, the retroperitoneal and those about the celiac axis, were considerably enlarged, edematous and hyperemic. Histologically, all showed moderate lymphoid hyperplasia and lymph sinuses engorged with moderate numbers of lymphocytes and mononuclear phagocytes. One node showed prominent foci of necrosis and autolysis. In most of the nodes the interfollicular lymphoid tissue was especially abundant.

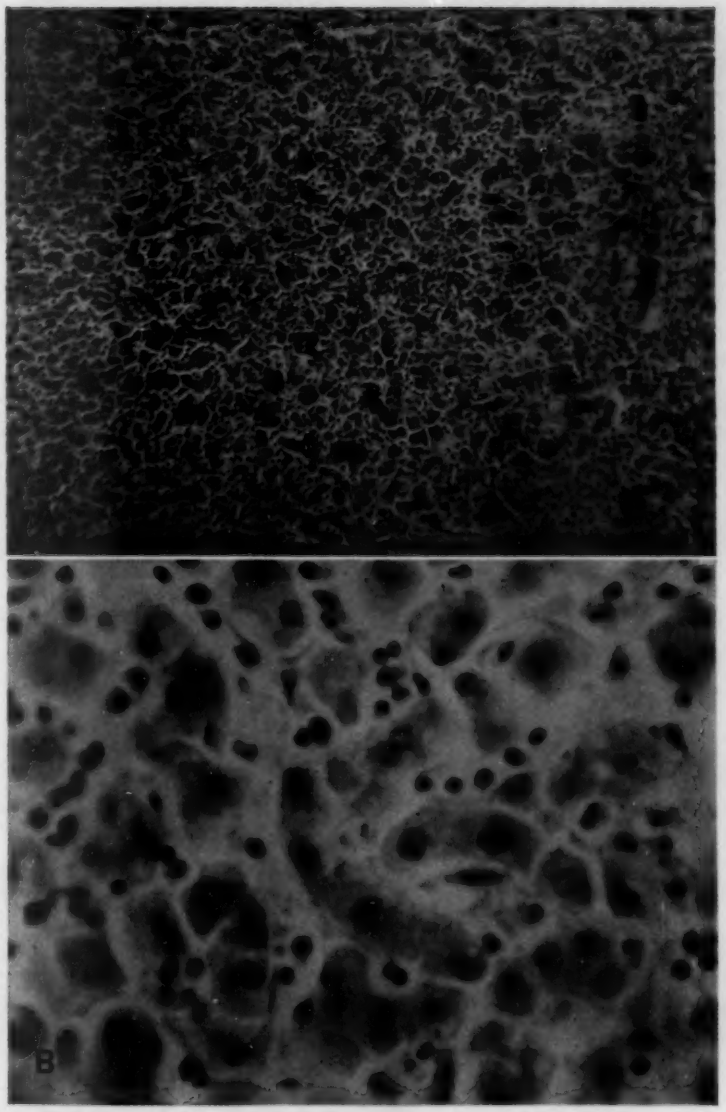

Fig. 1.—*A*, liver in case 3. Many of the liver cells are swollen. Nearly all are detached from one another, frequently disrupting the continuity of the hepatic cell cords. Prominent numbers of lymphocytes and monocytes diffusely infiltrate the stroma. Changes are most marked in the central and midzonal areas. (× 50.)

B, higher magnification of *A*. (× 550.)

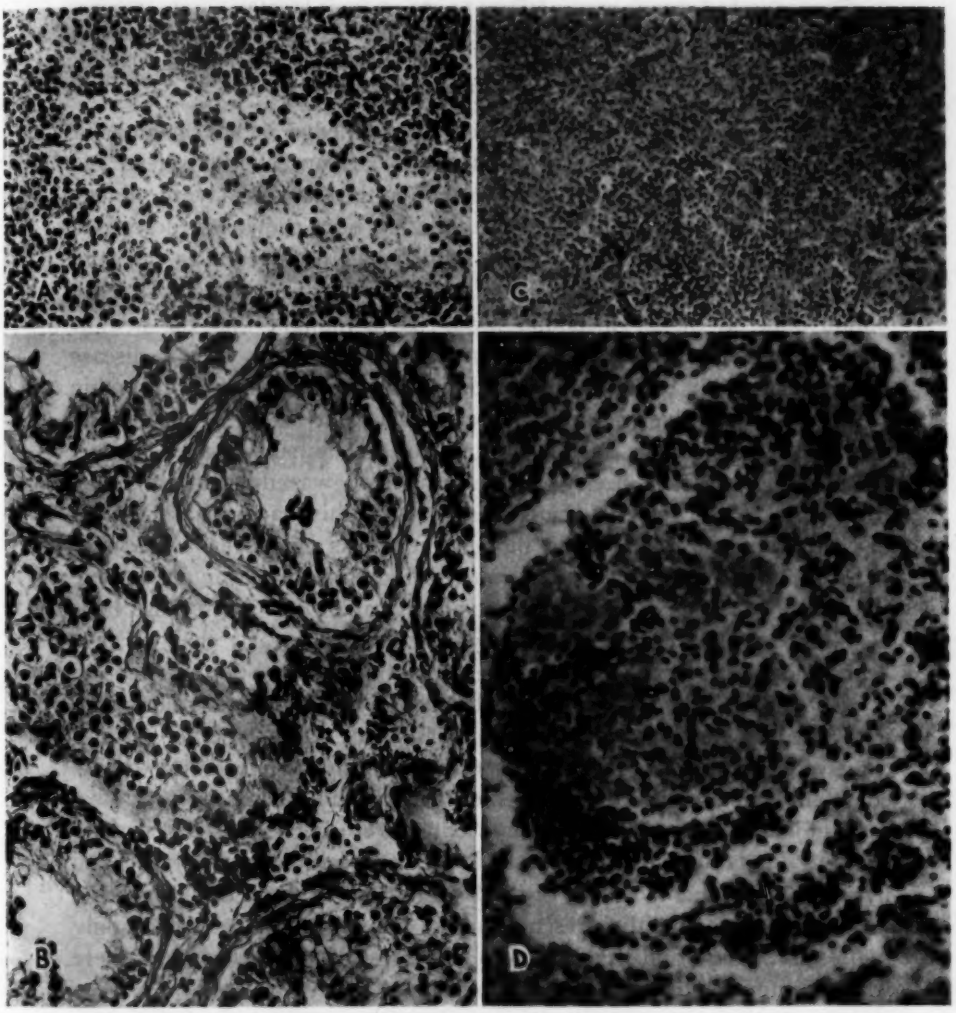

Fig. 2.—*A*, spleen in case 3. Centrally there is a large area of edema. Note the marked lymphocytic infiltration of the adjacent tissue. (× 85.)

B, orchitis with arrest of spermatogenesis in case 3. Moderate numbers of lymphocytic cells infiltrate the stroma. The spermatic tubules are devoid of healthy sperm. (× 85.)

C, liver in case 7. Diffuse necrosis and autolysis of liver cells involves all except a few of the peripheral lobular cells. Autolysis is not complete. Dead remaining liver cells and cellular debris are stained prominently with eosin. Throughout is a diffuse lymphocytic infiltration of the stroma. (× 122.5.)

D, lymph node from the hilus of the liver in case 7. Necrosis of a germinal center is associated with a mild infiltration of polymorphonuclear leukocytes. (× 234.)

The common bile duct contained thin, pale orange bile and showed no anatomic abnormalities. The portal vein was intact and contained thin fluid blood.

The anatomic diagnosis was as follows: acute epidemic hepatitis; acute splenitis; subcapsular splenic hemorrhage with laceration of the capsule; hemoperitoneum (2,800 cc.); acute regional lymphadenitis; acute interstitial pneumonitis; orchitis; myocarditis; jaundice; mild fatty degeneration of the kidneys.

This is not only the first case to my knowledge in which epidemic hepatitis was complicated by spontaneous rupture of the spleen but the first one in which death occurred on the second day of illness, at a much earlier stage of the disease than has been previously described. The only hemorrhagic phenomenon which had occurred was the subcapsular splenic hemorrhage. Unfortunately, it was not possible to obtain data on the prothrombin level. It is thought that the hemorrhagic phenomena so frequently seen in the later stages of this disease are most probably related to diminution of the formation of prothrombin by the damaged liver. In this case, however, it seems probable that the underlying factor in the production of the subcapsular hemorrhage may well have been the splenitis which was demonstrated histologically. The hepatic changes shown in this early phase of the disease are of interest. Even though there was evidence of extensive hepatocellular damage, autolysis was still minimal. Of interest were the occasional plugs of bile within the biliary canaliculi. Such plugs have also been noted by others in those few cases in which early changes have been studied either at postmortem examination or at aspiration biopsy. It is thought that this mechanical obstruction of the intralobular canaliculi may be a most important cause of persistence of jaundice. Testicular changes characterized by arrested spermatogenesis have been noted quite commonly but not universally by other writers; and it has been concluded that the hepatic damage must be not only severe but extensive and long standing. It is thought that arrest of spermatogenesis in cases of hepatic liver damage is due to failure of the liver to destroy estrogens circulating in the blood. Yet in the present case the known illness had lasted only two or three days and in addition to the arrest of spermatogenesis there was definite orchitis (fig. 2*B*). Swollen regional lymph nodes are quite characteristic, particularly in those cases with a duration of less than one month.[14a] It has been thought that the edema, the acute hyperplasia and the acute lymphadenitis may be representative of a reaction secondary to the destruction of large areas of the liver. In this particular case the concomitant acute splenitis and acute interstitial pneumonitis, along with the other lesions, is highly indicative of a virus disease. In the various reports on hepatitis which I have seen this is the first in which interstitial pneumonitis has been described as outstanding and seemingly a part of the systemic disease. Descriptions of splenic lesions in such early stages of hepatitis are rare, and in no

instance described had the splenic changes been as pronounced as in this case. Histologically, there was true splenitis with focal areas of edema. Splenic changes of the same order but less pronounced were observed in cases 7 and 8, in which also relatively early lesions of hepatitis were observed.

FATAL ACUTE EPIDEMIC HEPATITIS OCCURRING IN WOUNDED MEN IN WHOM THE ICTEROGENIC AGENT WAS POSSIBLY INTRODUCED BY TRANSFUSIONS OF WHOLE BLOOD OR PLASMA

Five of our patients showed a remarkable coincidence of history in that all 5 had been wounded three months previously on the same battlefield, had received multiple transfusions of blood and plasma, had been in contact with no one known to have hepatitis and had become ill at about the same time. A sixth (case 1) had also been wounded three and a half months previously and undoubtedly had been given transfusions but is not included in this group inasmuch as records of treatment at the advanced base hospital where he was originally treated are not available.

The acute hepatitis following transfusions of whole blood, plasma, convalescent measles serum and biologic products containing human serum (the original yellow fever vaccine used early in 1942) is well recognized in the literature. It is felt by the majority of workers that it is in reality produced by a filter-passing icterogenic agent which is closely related to, if not identical with, that which is the cause of acute epidemic hepatitis.

Inasmuch as the 5 patients whose cases are to be reported in the following pages had not been in known contact with persons presenting clinical jaundice, and inasmuch as the intervals of time which elapsed after the first blood transfusions following their wounds averaged three months, it seems probable that the icterogenic material in their cases was introduced intravenously. Clinically, the hepatitis of these patients was striking in the absence of the usual preicteric phase, the short duration and the severity once the disease had become manifest.

The hepatic damage was of the same type in all and classically was that of acute epidemic hepatitis, producing a histologic picture similar to that seen in so-called acute yellow atrophy. Acute splenitis, regional lymphadenitis, orchitis and variable but mild cholemic nephrosis occurred in the majority. Cerebral lesions were minimal, variable and characterized chiefly by small perivascular hemorrhages of focal distribution.

CASE 4.—This patient was a private first class in the United States Marine Corps, 21 years of age. The duration of his hepatitis was nine days. His complaint was multiple wounds of the face with stenosis of the mouth, lasting three months, and nausea and vomiting, one day.

The patient was wounded on Iwo Jima Feb. 28, 1945, and was admitted to the United States Naval Hospital, Oakland, Calif., June 1. He had suffered a loss of the greater portion of his lower and upper jaws and part of his nose. After his injury he had been given many units of whole blood and plasma. At the time of his arrival here the opening of the mouth had closed down with scar tissue so that it was stenotic, consisting of a circular hole approximately one-half inch in diameter. On the second day after his admission he became nauseated and vomited.

The rectal temperature was 100 F., the pulse rate 76, and the respirations 18 per minute. Until the onset of nausea and vomiting physical examination gave essentially negative results except for deformity of the face, stenosis of the mouth, considerable loss of weight and moderate dehydration. He was ambulatory and remarkably cheerful in view of the extent of his injury.

Nausea and vomiting continued in spite of intravenous therapy with dextrose, amigen sol, Betalin Complex [21] and thiamine hydrochloride. In view of the constant nausea and vomiting it was recognized that the stenotic oral opening imposed a constant risk of aspiration pneumonia. The liver and the spleen were at no time palpable. There was consistently mild leukopenia. On June 4 the white blood cell count was 5,550 cells per cubic millimeter, 59 per cent being polymorphonuclear leukocytes. Two days later, it was 4,850, with 55 per cent leukocytes, and the icterus index was 121.7 units. The serum protein on June 4 was 6.5 Gm. per hundred cubic centimeters, and the blood sedimentation rate was 2. On the evening of June 8 the patient lapsed into coma. His vomiting ceased after a period of extreme restlessness and delirium. The following morning he was in deep coma. His temperature was 99 F., pulse rate 100, respirations 10 per minute and blood pressure 130 systolic and 90 diastolic. The abdomen was soft; the liver and the spleen continued to be nonpalpable. Both lower extremities were somewhat spastic, with hyperactive reflexes. There had developed since the preceding evening bilateral ankle clonus, and the Babinski reflex had become positive. The abdominal and cremasteric reflexes were absent. His blood serum had a definite greenish color, due possibly to biliverdin. By the morning of June 10 his temperature had risen to 107 F. rectally; his respirations had become labored and their rate was up to 48; the pulse rate was 150. The abdomen continued to be soft. Several convulsions occurred at intervals. The pupils were dilated, the right arm was spastic, the legs were flaccid, and the Babinski reflex had now become negative. Deep reflexes were not elicitable. The prothrombin percentage had dropped to 27. He remained in coma and died at 4 p. m.

The clinical diagnosis was acute infectious jaundice with possible free intracranial bleeding.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed moderate chrome yellow icterus. The liver was moderately shrunken and weighed 1,120 Gm. It was flabby and possessed a slightly wrinkled, pale brown capsule. Flabbiness was especially marked in the left lobe. On cut section the parenchyma showed a pale tan, ischemic, mottled surface in which it was thought that lobular markings were still evident. There were a few areas, however, where the tissue was purplish red except for small oval islands of pale tissue measuring up to 0.3 cm. Except for a few small islands histologic sections showed almost complete ablation of liver cells. Those liver cells which persisted were perilobular

21. Betalin Complex (Vitamin B Complex, Lilly) contains in 2 cc. 10 mg. of thiamine hydrochloride, 4 mg. of riboflavin, 150 mg. of nicotinamide, 5 mg. of pantothenic acid (as calcium pantothenate) and 10 mg. of pyridoxine hydrochloride (vitamin B_6 hydrochloride).

in distribution. Generally, hepatocellular necrosis and autolysis of liver cells dominated the histologic picture. Occasional small groups of lymphocytic cells infiltrated the stroma.

The spleen was slightly enlarged, weighed 258 Gm. and showed moderate hyperemia. Its pulp was firm, brownish red and slightly opaque, and its stroma was focally infiltrated by a few small collections of lymphocytes, phagocytes and polymorphonuclear leukocytes. Malpighian bodies were distinct, and histologically a few were infiltrated by polymorphonuclear leukocytes. Pale brown bile was contained in the extrahepatic biliary passages and in the gallbladder.

Each lung showed moderate aspiration pneumonia.

The brain revealed no gross or histologic lesions of significance except hyperemia.

The testes showed histologically mild but definite arrest of spermatogenesis.

The anatomic diagnosis was acute epidemic hepatitis, mild arrest of spermatogenesis, splenitis, lymphadenitis of the original nodes and bilateral aspiration pneumonia.

CASE 5.—A gunnery sergeant in the United States Marine Corps, 24 years of age, had hepatitis for seven days. His complaints were chilliness, nausea and vomiting lasting four days and jaundice one day.

The patient had been wounded in the abdomen on Iwo Jima March 2, 1945. His abdomen was opened three hours later, and three jejunal perforations were sutured. He was given whole blood and penicillin, and other supportive treatment was used. He was evacuated via several naval activities to the United States Naval Hospital, Oakland, Calif., where he was admitted for the first time May 2, 1945. His condition was good, the wound had ceased draining, and on May 12 he was given a week's convalescence leave and transferred to a convalescence hospital on June 8, at which time he felt well. Three days later, however, a temperature of 100.2 F. was recorded, and he complained of chilliness, nausea and vomiting. An early stage of intestinal obstruction was suspected, and he was treated with sulfadiazine, and other general measures were instituted. The symptoms continued until June 15, when icterus appeared and he was transferred as a readmission patient to this hospital with the diagnosis of probable intestinal obstruction.

His temperature was 97.6 F., pulse rate 120 and respiratory rate 24. The skin, the scleras and the mucous membranes showed moderate icterus. The patient was restless and disoriented and did not respond to questions. Otherwise the physical examination showed only distention of the urinary bladder to the level of the umbilicus and suggestive bilateral positive Babinski reflexes.

His treatment consisted of intravenous injections of dextrose, amigen, vitamin B complex and choline, with supportive measures. His icterus index was 104, and the reaction to the cephalin cholesterol flocculation test was 3 plus. On June 17 his prothrombin percentage was 45.5. His delirium and semicomatose condition persisted. On June 18 he lapsed into deep coma and died. For a day prior to death the following signs were noted: The pharyngeal reflex was absent; the biceps and achilles tendon reflexes were not obtained; the knee jerks were hypoactive; superficial reflexes were absent, and there was no response to painful stimuli.

The clinical diagnosis was acute infectious hepatitis due possibly to serum transmission of the icterogenic agent.

Pathologic Observations.—Liver tissue obtained for biopsy with a Vim-Silverman needle revealed the classic microscopic changes of acute epidemic hepatitis. There had occurred extensive autolysis of the central and midzonal liver cells. Those which persisted peripherally in the lobules were quite frequently swollen, were detached from one another and contained finely vacuolated cytoplasm. Peripherally

in the lobules biliary canaliculi were occasionally dilated and contained yellowish plugs of bile. Very occasionally small groups of lymphocytes with a few polymorphonuclear leukocytes infiltrated the supporting stroma. There was preservation of the sinusoids and the stroma. The wall of one central venule had been infiltrated by numerous lymphocytes. In the areas of greatest damage Kupffer cells were prominently laden with lipochrome pigment.

The anatomic diagnosis was acute epidemic hepatitis.

CASE 6.—The patient was a private first class, white, in the United States Marine Corps, 22 years of age. The duration of his hepatitis was seven days.

He was admitted to the United States Naval Hospital, Oakland, Calif., June 10, 1945, at which time his condition was good except for afternoon elevation of temperature and anorexia. March 3, 1945 he had been wounded on Iwo Jima, at which time he had sustained a perforation of the cecum and a wound of the right buttock. The cecum was exteriorized, following which a retroperitoneal abscess developed.

His temperature was 100 F., pulse rate 100 and respiratory rate 18. His general condition was good. There were present a healed bullet wound of entrance in the upper part of the right buttock and a functioning cecostoma in the right iliac region at the upper margin of a granulating incision. An opening in the lower part of the incision communicated with a large abscess in the right iliac fossa and a draining sinus extending to a small wound in the right flank.

The anorexia which the patient had on admittance persisted. Eight days later, on the morning of June 18, the patient suddenly lapsed into severe shock and coma. His pulse was rapid and his respirations were shallow. Slight jaundice of the scleras was noted for the first time. The abdomen was soft and not tender. Supportive treatment was given, with slight transient improvement. A neurologic examination revealed some motion with painful stimuli, a slow bilateral ankle clonus and a bilateral positive Babinski reflex. Sucking and grasping reflexes were absent. The liver and the spleen were not felt. A diagnosis was made of acute atrophy of the liver, probably infectious hepatitis. Dextrose, amigen, Betalin Complex,[21] thiamine hydrochloride and nicotinic acid were given intravenously. His general condition continued to be poor. Deep reflexes in the lower extremities were no longer elicitable, and the patient died at 1:10 a. m., June 20.

The clinical diagnosis was acute yellow atrophy of the liver, most probably acute epidemic jaundice.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed mild icterus. Approximately 50 cc. of amber fluid with flecks of fibrin was contained in the peritoneal cavity. Within the right pleural cavity was 1,000 cc. of clear amber fluid.

The liver was small, shrunken, and weighed 1,135 Gm. Glisson's capsule was pale, purplish brown and relatively smooth except for a few slightly wrinkled and pitted depressed areas over the main lobe anteriorly. On cut section it showed a variegated tannish yellow to dark brownish red pattern, in which lobular markings were thought to be grossly evident (fig. 3*A*). There was much flabbiness of the left lobe. Histologically, the hepatic changes were classically characteristic of acute epidemic hepatitis. Except for a few, widely scattered, tiny islands of residual liver cells, there had been almost complete hepatocellular necrosis, but with preservation of lobular outlines. Small perilobular bile ducts were numerous, occurred in small groups and were more closely approximated to one another than usual as a result of extensive hepatocellular necrosis with "collapse" of lobules. Small groups of lymphocytes irregularly infiltrated the stroma as well as the walls of some of the central venules. Occasional phagocytes and reticuloendothelial cells

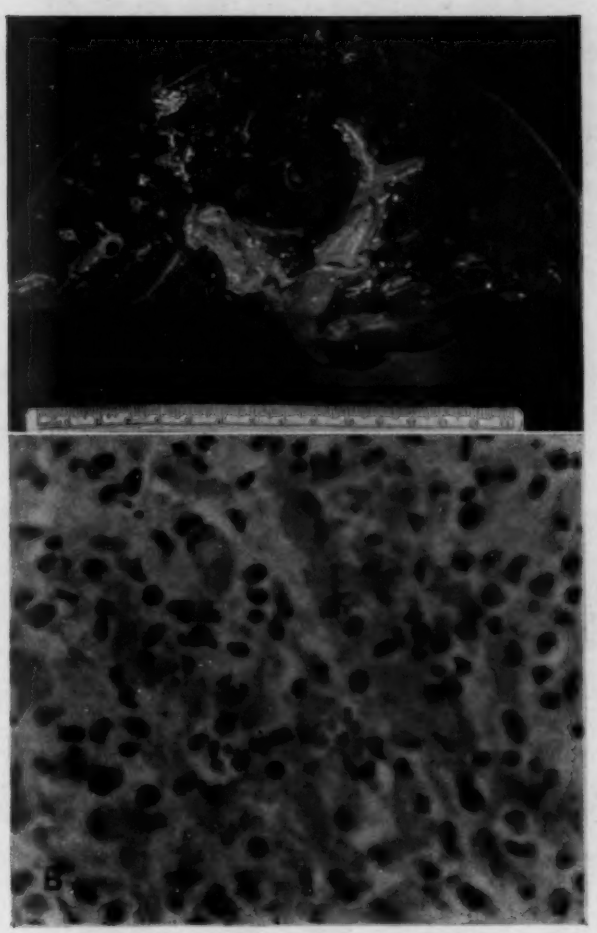

Fig 3.—*A*, liver in case 6. Grossly, the liver was small, shrunken, and weighed 1,135 Gm. There was no nodulation. The freshly cut surface showed a diffuse variegated appearance which suggested accentuated lobular markings.

B, liver in case 7. Faint outlines of necrotic liver cells with "coagulated" cytoplasm remain. Such cells are eosinophilic. Autolysis and removal of cellular debris is complete. (× 550.)

were prominently laden with yellowish lipochrome pigment. The lymph nodes at the hilus of the liver were large, spongy and pale tan. Small groups of cells, consisting of an admixture of lymphocytes and polymorphonuclear leukocytes, infiltrated the stroma and the lymph sinuses as well as a few germinal centers.

The spleen was moderately enlarged, weighed 325 Gm. and measured 17 by 10.5 by 4.5 cm. On cut section, the malpighian bodies were distinct, and the intervening pulp was firm but dark grayish brown (fig. 4). The latter was infiltrated by scattered small groups of lymphocytes and polymorphonuclear leukocytes. Terminal bilateral bronchopneumonia was associated with a serous effusion of 1,000 cc. in the right pleural space.

The testis, in addition to showing considerable arrest of spermatogenesis, showed mild infiltration of the stroma in the form of small focal collections of lymphocytes.

The brain showed numerous markedly congested small blood vessels in the white matter of the cerebrum, in the basal nuclei and the mesencephalon. Histo-

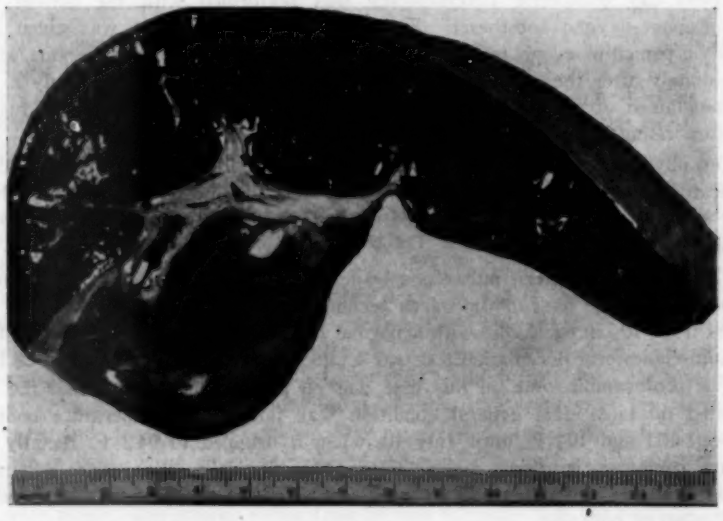

Fig. 4.—Spleen in case 6; weight 325 grams. The malpighian bodies are distinct. At autopsy the pulp was firm but dark grayish brown.

logically, aside from marked congestion of small blood vessels and occasional tiny perivascular hemorrhages, there were no significant lesions.

The anatomic diagnosis was acute epidemic hepatitis, acute splenitis, bronchopneumonia, pleural effusion, regional lymphadenitis, marked arrest of spermatogenesis, orchitis and gunshot wound of the abdomen.

CASE 7.—The patient was a sergeant of the United States Marine Corps, 23 years of age. The duration of his hepatitis was six days. He complained that he had suffered from a wound of the back with laceration of the ascending colon and a pelvic abscess for three and a half months and from nausea and pain in the upper abdominal region for one day.

He was admitted to the United States Naval Hospital, Oakland, Calif., June 10, 1945, having been wounded on Iwo Jima March 17, 1945. A bullet had entered the right side of the back just above the sacroiliac joint and had traversed the abdomen, lacerating the ascending colon, and having its point of exit just above

the anterior superior spine of the right ilium. Two days later the abdomen was surgically explored, and the lacerated ascending colon was exteriorized. The postoperative course was stormy, with signs of peritonitis. Improvement began about the tenth postoperative day. After operation he received intravenously dextrose, blood plasma and whole blood. April 5 an external closure of the colostoma was performed, and the subsequent course was satisfactory. The patient was transferred to a naval hospital in the Hawaiian Islands April 15, and April 27 a large retroperitoneal abscess on the right side was drained. He was transferred to the United States Naval Hospital, Oakland, Calif., by air June 10. On admission here examination showed an emaciated man complaining of two painful fecal fistulas, one the old colostoma, and the other a wound in the right lateral abdominal wall. He was febrile, with a daily temperature of 101 F. Roentgen studies revealed a large retrocecal abscess extending into the pelvis and communicating with the ascending colon. Determination of the serum protein showed 5.8 Gm. per hundred cubic centimeters. June 22 a transfusion of 100 cc. of whole blood was given, and the next day transverse ileocolostomy was performed with the patient under cyclopropane-oxygen anesthesia. Following this procedure, he was given 20,000 units of penicillin every two hours for the next six days. He became afebrile immediately after the operation, and his general condition improved July 5, when he complained of nausea, pain in the upper abdominal region and fever, his temperature rising to 104 F.

On physical examination his temperature was 102.4 F., pulse rate 95 and respiratory rate 20. The scleras, the skin and the mucous membranes showed mild icterus. There was diffuse tenderness of the abdomen to deep palpation but no abdominal rigidity.

The patient was given intravenously dextrose, vitamin B complex and amigen. At no time did the liver or the spleen become palpable. The white blood cell count varied from 10,750 to 15,200, with a normal differential count. The reaction to the cephalin-cholesterol flocculation test was 4 plus. The icterus index rose to 28.1 July 9. The prothrombin time on this date was 88 per cent of normal, and the urine revealed no bile. His general condition was fair. His temperature continued between 103 and 104 F. until July 10, when it dropped to 94.2 F. rectally. He became comatose, irrational and restless. Neurologically, there were generalized motor weakness and absence of reflexes. He died on the following day, July 11, in circulatory collapse.

The clinical diagnosis was acute infectious jaundice.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed mild icterus. The liver weighed 1,475 Gm. In the left lobe, there was much flabbiness of the parenchyma, and the overlying Glisson's capsule was slightly wrinkled—otherwise the capsule was smooth. On cut section, lobular markings persisted, and there was present a uniform mottled appearance with narrow tannish yellow streaks of tissue surrounding dark brownish red oval islands centrally. Histologically, diffuse changes were characterized by subtotal necrosis and autolysis of the liver cells. There persisted in scattered foci outlines of "coagulated" liver cells with no nuclear staining (figs. 2*C* and 3*B*). The presence of such "dead" cells indicated incomplete removal of cellular debris in contrast to many of the other cases, in which the process had been completed.

The spleen was moderately enlarged and weighed 400 Gm. It was flabby, and on cut section its pulp was slightly opaque, rather soft and brownish red. The malpighian bodies were small and faintly visible through the slightly swollen, opaque surface. Microscopically, however, the malpighian bodies were distinct.

Many showed much edema centrally and were infiltrated in such areas by moderate numbers of poorly preserved polymorphonuclear leukocytes. Occasional malpighian bodies showed necrosis of the germinal centers. Many small groups of lymphocytic cells with occasional polymorphonuclear leukocytes and mononuclear phagocytes infiltrated the pulp.

The testes were grossly normal but histologically showed moderate to marked arrest of spermatogenesis. Occasional small groups of lymphocytes infiltrated the stroma, and about such areas there was mild edema.

The regional lymph nodes were markédly enlarged, measuring up to 3.5 cm. in width, and were edematous. On cut section they had a swollen, mottled tan appearance. Microscopically, the lymphoid follicles were large, and a number of their swollen germinal centers contained small foci of necrosis (fig. *2D*). Other germinal centers were epithelioid in appearance and bounded by only a narrow zone of lymphocytic cells. The lungs were normal except for a small tannish white area in the left lung, which microscopically showed interstitial pneumonitis of moderate degree. The brain was essentially normal except for marked congestion of small blood vessels in the white matter of the cerebrum, in the basal nuclei and in the mesencephalon.

The anatomic diagnosis was: acute epidemic hepatitis; acute splenitis; acute lymphadenitis of the regional lymph nodes; interstitial pneumonitis; orchitis with arrest of spermatogenesis; multiple old wounds of the abdomen.

CASE 8.—The patient was a private first class of the United States Marine Corps, 19 years of age. The duration of his hepatitis was six days. He complained that he had suffered from multiple shrapnel wounds of the pelvis four months and jaundice one day.

This patient was admitted to the United States Naval Hospital, Oakland, Calif., April 14, 1945, having been wounded on Iwo Jima Feb. 19, 1945. He sustained multiple wounds of the pelvis, resulting in a ureterorectal fistula, two cutaneovesicular fistulas and an injury to the lower part of the bowel. As a consequence of these injuries suprapubic cystostomy and colostomy were performed. The postoperative course and convalescence were slow but progressive. June 4 the patient began to complain of pain of the upper part of the abdomen. Because of the persistence of the abdominal pain it was thought that hepatitis might possibly be developing, and tests were made: The icterus index June 14 was 6.3 units, and the cephalin-cholesterol flocculation test gave a result of 2 plus June 15 and June 17. For the next month the patient had no complaints, and his general condition changed very little. July 11, however, he became deeply jaundiced and drowsy but was mentally clear.

There were no unusual findings on physical examination except for hyperactive reflexes and bilateral ankle clonus. His temperature was 98 F., pulse rate 100 and respiratory rate 20. The scleras, the skin and the mucous membranes showed deep icterus.

The patient was given intravenously dextrose, amigen sol, Betalin Complex,[21] thiamine hydrochloride and nicotinamide. The following three days his condition remained about stationary. He then became drowsy, and his temperature varied from 101 to 103 F. He was given a transfusion of whole blood but failed to improve. He remained mentally alert. July 16 moderate respiratory distress developed, and a few coarse rales were heard at the base of each lung. Chills also occurred, and the next day the patient suddenly died.

The clinical diagnosis was acute hepatitis.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed moderate chrome yellow icterus.

The liver was normal in size and weighed 1,727 Gm., but was flabby in consistency. Glisson's capsule was pale brown and slightly wrinkled over the posterior aspect of the lesser lobe, which appeared considerably less thick than normal. Beneath the capsule, the lobular markings appeared distinct, even accentuated, and there was a definite mottled appearance with small, oval, reddish brown islands surrounded by pale yellowish parenchyma. This appearance was not uniform, however, inasmuch as large, opaque, swollen, grayish brown areas in the dome of the main lobe showed complete absence of lobular outlines. Histologically, there was extensive autolysis of liver cells, which involved chiefly the midzonal and central lobular areas. Moderate numbers of liver cells remained, and these were large, swollen and stained poorly. Rather numerous lymphocytes diffusely infiltrated the stroma of the lobules and the walls of the central venules. Among these were occasional polymorphonuclear leukocytes. A moderate number of Kupffer cells were laden with yellowish lipochrome pigment.

The spleen was moderately enlarged and weighed 517 Gm. Its capsule was tense and tore readily on removal of the organs. The pulp was slightly edematous, semiliquid, dark brownish purple and slightly opaque. Malpighian bodies were prominent. Microscopically, there was extreme congestion of the pulp. The malpighian bodies were rather indistinct, and a number showed necrosis of their centers.

The testes were rather small, weighing 13 and 16 Gm., respectively, and microscopically showed marked diffuse arrest of spermatogenesis with a mild degree of orchitis, characterized by tiny focal infiltrations of lymphocytes.

The lymph nodes at the hilus of the liver were greatly enlarged and spongy and measured up to 4.0 cm. in width. Histologically, they showed moderate to marked edema. The germinal centers of the lymphoid follicles were indistinct, and a few showed mild necrosis accompanied by a mild to moderate infiltration of polymorphonuclear leukocytes.

The brain was essentially normal except for marked congestion of small blood vessels in the basal nuclei, the mesencephalon and the white matter of the cerebrum.

Ecchymotic hemorrhages occurred beneath the epicardium and the endocardium.

The anatomic diagnosis was acute epidemic hepatitis; acute splenitis; acute lymphadenitis of the regional lymph nodes; orchitis with arrest of spermatogenesis; multiple old wounds of the pelvis with a rectoureteral fistula and pyelonephritis.

An interesting feature of this case is the fact that the cephalin-cholesterol flocculation test was positive on two occasions one month before the advent of clinical jaundice. This observation suggests the value of this test when obscure abdominal complaints, even though minor, develop in previously wounded men. In a companion paper Snell, Wood and Meienberg [22] pointed out that this test is of value in detecting the presence of hepatic damage in the incubation period and the preicteric phase. They pointed out further that when the test is positive under such circumstances the administration of gamma globulin may be of distinct value at that time in attenuating or aborting clinical development of the disease.

22. Snell, A. M.; Wood, D. A., and Meienberg, L. V.: Infectious Hepatitis with Especial Reference to Its Occurrence in Wounded Men, Gastroenterology **5**: 241, 1945.

MISCELLANEOUS CASES OF EPIDEMIC HEPATITIS

The last 2 cases in this series conform more closely to the recognized clinical picture of epidemic hepatitis, especially as regards duration of the disease. In contrast to the preceding 5 cases, the clinical course in each of these cases (in retrospect) showed well defined preicteric, intermediate and final phases. Even though the symptoms were classically referable to the abdomen, these 2 cases presented diagnostic difficulties, as well as interesting necropsy findings. In 1 case the condition seemed to be improving clinically when a sudden abdominal episode, most probably secondary to an unrecognized intercurrent attack of bacterial endocarditis, caused a critical turn for the worse, with death occurring in a few days. The 2 cases presented the most protracted clinical courses noted in this series and at autopsy showed nodulation of the liver with histologic lesions indicative of recrudescence.

CASE 9.—The patient was a chief machinist's mate in the United States Navy, 28 years of age. The duration of his hepatitis was sixty-two days. He complained of weakness and fatigability for three weeks and of anorexia, jaundice, abdominal distress and clay-colored stools for two weeks.

For three weeks, beginning about Nov. 20, 1943, there had been a gradual onset of weakness and fatigability. One week after onset jaundice developed along with anorexia, epigastric distress and clay color of stools. The patient was admitted to the sick list while attached to his ship and was transferred to a United States naval hospital December 10, with the diagnosis of acute infectious jaundice.

His temperature was 99 F., pulse rate 80 and respiratory rate 20. There was a marked jaundice of the skin, the scleras and the mucous membranes. The abdomen revealed no abnormality except for tenderness along the left costal margin and in the midepigastrium.

The jaundice, which was marked, did not recede. The icterus index, which was 187 units on the day of entry, gradually reached 266 on Jan. 12, 1944. During this time his blood showed leukopenia, with leukocyte counts ranging from 5,400 to 6,450. Roentgenograms revealed an extrinsic duodenal shadow interpreted as representing a possible lesion of the pancreas. Ascites became apparent on January 12. Exploratory laparotomy was decided on. However, January 19, the day before he was scheduled for operation, a sudden epigastric pain developed and the abdomen became rigid. Emergency laparotomy was performed, local anesthesia being used, and 3,000 cc. of ascitic fluid was removed. Inspection of the liver revealed multiple dark nodules interpreted by the surgeon as "melanosarcomatous." The postoperative course was rapidly downhill, the patient becoming comatose and dying two days later, January 21.

The clinical diagnosis was metastatic melanosarcoma of the liver, with obstructive jaundice.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed marked icterus. Contained within the peritoneal cavity was 1,000 cc. of slightly turbid, blood-tinged fluid. Both layers of the peritoneum were markedly hyperemic and in places fiery red.

The liver was markedly flattened and flabby and weighed 860 Gm. Glisson's capsule was especially wrinkled over the main lobe. On cut section there was a contrast between the two lobes. The right lobe presented a mottled purplish

red to orange appearance, with absence of lobular markings, and the left lobe a homogeneous, pale, brownish tan appearance, with indistinct lobular markings. On the posterior aspect near the hilus, as well as in the caudate and quadrate lobes, there were indistinct greenish tan nodular areas which measured up to 1.5 cm. in width. These showed lobular markings. The surrounding liver tissue was flabby and brownish red. Several histologic sections showed complete absence of liver cells. Residual groups of small perilobular bile ducts were numerous. Tiny groups of lymphocytes were scattered throughout. Other sections showed faint outlines of the lobule with an attempt at liver cell regeneration. However, most of the liver cells were uniformly swollen, granular and devoid of nuclear staining.

The spleen was moderately enlarged, weighed 260 Gm. and measured 17 by 10 by 3 cm. Its pulp was soft and slightly opaque and presented a mottled brownish gray appearance. Histologically it showed marked hyperemia.

The heart had numerous recent friable vegetations on both leaflets of the mitral valve. There was but slight fibrous thickening of the leaflets. Histologic sections of the valve showed recent bacterial endocarditis, which was associated with extensive hemorrhagic extravasation beneath the adjacent endocardium.

The testes were rather small and microscopically showed marked arrest of spermatogenesis.

The anatomic diagnosis was: acute epidemic hepatitis with jaundice; mild arrest of spermatogenesis; acute bacterial endocarditis of the mitral valve.

Case 10.—The patient was a chief radioman in the United States Navy, 23 years of age. The duration of his hepatitis was uncertain but was estimated to have been approximately forty-seven days. The complaint was generalized intermittent abdominal pain lasting ten days.

In November 1943 the patient had been admitted to another naval hospital with the diagnosis of gastritis. He was discharged to duty on December 8. Several days before Christmas, abdominal pain of an intermittent nature developed, which was generalized over the whole abdomen. On the day the patient entered the hospital, December 31, the pain had localized in the right lower quadrant of the abdomen, and the patient vomited twice.

His temperature was 102.4 F., pulse rate 68 and respiratory rate 24. He was well developed but appeared acutely ill and was rather stuporous. His abdomen was slightly distended and presented boardlike rigidity, with generalized tenderness, which was most marked in the right lower quadrant. Peristalsis was markedly diminished.

It was the opinion of the examining surgeons that he had generalized acute peritonitis secondary either to rupture of the appendix or to peptic ulcer. Three days later, the scleras became icteric, the abdomen remained distended, and his temperature fluctuated from 101 to 104 F. On January 4 the abdominal distention was less, and spasm of the abdominal muscles was absent. Severe anemia rapidly developed. The red blood cell count, which was 4,210,000 on December 31, dropped to 1,560,000 on January 4. The white cell count varied from 6,200 on December 31 to 9,100 on January 5. Transfusions of whole blood were given. On the following day, ascitic fluid was detected, and 500 cc. was removed. Two days later, January 7, the abdominal distention became more marked, rales developed at the base of each lung, and the patient died eight days after entering the hospital. His icterus index had varied from 50 to 111 units.

The clinical diagnosis was acute peritonitis and jaundice of uncertain origin, possibly secondary to perforation of acute appendicitis.

Pathologic Observations.—The skin, the scleras and the mucous membranes showed marked icterus. The right breast weighed 56 Gm. and showed moderate gynecomastia. Contained within the peritoneal cavity was 4,600 cc. of icteric ascitic fluid.

The liver weighed 1,890 Gm. Glisson's capsule was irregular in contour owing to coarse underlying nodulation. The parenchyma was divided into faintly perceptible nodules, which varied from 0.7 to 0.9 cm. in width. It was icteric and brownish orange. Lobular markings were indistinct. There was demonstrable increase in fibrous tissue on cut section. Microscopically, nodules of hyperplastic liver tissue were separated from one another by nonhyalinized fibrous stroma, which contained many groups of proliferating perilobular bile ducts. Small groups of lymphocytes were scattered throughout. Some of the liver cells were large, stained poorly and were detached from one another. In some areas necrosis of liver cells was extensive. In some sections it involved chiefly the central and midzonal portions of the lobules, although some lobules were completely involved.

The spleen weighed 585 Gm. and measured 20 by 12 by 5.5 cm. Its pulp was firm and reddish brown. Histologically, the pulp was markedly engorged with blood.

The testes showed moderate atrophy of the seminiferous tubules with subtotal arrest of spermatogenesis.

The anatomic diagnosis was as follows: acute epidemic hepatitis with areas of regeneration and secondary necrosis; ascites; moderate arrest of spermatogenesis; gynecomastia.

COMMENT

Four fairly distinct groups of cases are presented in this series of 10 fatal cases of epidemic hepatitis. In 2 cases mental and neurologic disturbances dominated the clinical picture. Such disturbances were present though not dominant in the terminal stages of nearly all the other cases (see table). Spontaneous rupture of the spleen with fatal hemoperitoneum occurred in 1 case on the second day of illness, affording an opportunity to study necropsy material at an unusually early stage of the disease. In 5 wounded men an unusually virulent or overwhelming type of hepatitis developed (third group of cases). In this group the possibility could not be excluded that the icterogenic agent had been introduced by transfusion of whole blood or plasma within an interval varying from three to three and a half months previously. Not only was the course uniformly much more rapid than usual, but the classic preicteric phase of symptoms was either absent or masked by conditions referable to the wounds which these patients had sustained. All had acute diffuse lesions of the liver, and again an opportunity was afforded of studying the tissue changes at earlier stages in this disease than has been possible with the more common, less overwhelming infections, which the patients survive considerably longer. The fourth group in this series consisted of 2 cases in which the clinical course and findings conformed more closely to those noted in other outbreaks of the disease. These 2 patients were the only ones who survived longer than ten days. Symptoms were referable primarily to the abdomen. In 1, in whom the

illness lasted about forty-seven days, hepatic lesions were revealed which were highly indicative of a recurrence superimposed on a considerable degree of regeneration. The liver of each patient showed nodulation in contrast to those of the other 8 patients in which the hepatic lesion was early, diffuse and free of nodulation.

An unusual feature of the clinical course in 8 cases was the brevity of the preicteric phase; either it was absent or it was masked by other conditions. Ordinarily, the course of fatal hepatitis falls into three phases: preicteric, intermediate and fatal. In the majority of cases the preicteric phase lasts seven days or less, although it may last as long as eighteen. Havens,[23] in reporting a series of 200 clinical cases in the Middle East, stated that 83.5 per cent showed a definite preicteric phase, which varied from one to eighteen days, with an average of five days. In the army series of 125 fatal cases reported by Lucke[14a] the preicteric phase varied from one to seventeen days, being in the majority seven days or less.

The intermediate phase in the present series of cases was likewise characterized by its brevity, lasting only seven days or less in the majority of instances. This is in contrast to representative data published elsewhere. For example, in Havens'[23] series it varied from four to eighty-three days, with an average of twenty-seven days. In Lucke's[14a] series it varied from three to forty-three days and in the majority of cases it lasted twenty-six days or less.

The striking brevity of the clinical course in the present series of cases no doubt accounts for the fact that in 80 per cent nodulation of the liver was either absent or barely perceptible and for the fact that the histologic lesions were observed at a much earlier stage than has been generally seen heretofore. In a few of the cases a mottled pattern of the freshly cut surface characteristic of lobular outlines persisted. On gross inspection the chief findings at the early stage were flabbiness of the liver, variable slight wrinkling of Glisson's capsule and variable decrease in weight. In a majority of the cases the liver possessed the consistency of a wet rag but on cut section showed persistence of lobular markings (fig. 3*A*). The lesions, therefore, were diffuse. By contrast, only in cases 9 and 10, in which the clinical course was longest, was the liver nodular. Typically the clinical picture in the intermediate phase gives no indication as to whether or not the disease is going to run its usual benign course. In a majority of the cases the icteric phase was so short and the patients so ill that a clearcut transition between the intermediate and the final phase was not apparent. Ordinarily the final phase is ushered in by a sudden dramatic change for the worse. Lucke[14a] noted

23. Havens, W. P.: J. A. M. A. **126**:17, 1944.

that death usually occurs within ten days after the onset of the final phase, and in his series there was a spread varying from two to eighteen days.

Pathologic Anatomy.—(*a*) Liver: The size of the liver, the presence of ascites, the size of the spleen and the complications are shown in the table. In 50 per cent of the cases the liver was definitely shrunken, possessing a weight of 1,135 Gm. or less. In no instance did it weigh in excess of 1,890 Gm. Generally, normal weight of the liver was observed in cases in which death occurred in the earliest stages of the disease or in cases of longer duration in which regenerative hyperplasia had occurred. The most characteristic finding was flabbiness of the hepatic parenchyma, which was noted even though a mottled pattern of lobular markings frequently persisted. In the 2 cases in which survival was longest the parenchyma was nodular, owing in part to irregular distribution of the lesions within the liver and in part to attempted regeneration of liver cells. In these older cases was seen also the greatest degree of bile duct proliferation. Microscopically, in most of the cases there were classic changes, characterized by diffuse hepatocellular necrosis and autolysis, predominantly central and midzonal, variable degrees of endophlebitis involving the central venules and rapid removal of cellular debris. Infiltration with inflammatory cells in variable degrees, chiefly lymphocytes, was evident in all cases. In spite of hepatocellular necrosis there was retention of lobular structure and no scarring. Hepatocellular necrosis had not progressed to diffuse autolysis of liver cells in 2 cases. In case 3, in which death occurred in an extremely early stage, possibly on the second day of illness, only a few liver cells had autolyzed. There was, however, extensive alteration in the lobular structure. Most of the liver cells were large, swollen and detached from one another. Comparatively few liver cells, however, had disappeared. An inflammatory component characterized by infiltrating lymphocytes and mononuclear phagocytes was diffuse and more extensive in this case than in any of the others (fig. 1*A*). In case 7, in which death occurred on the sixth day, the hepatic lesion was slightly more advanced. Hepatocellular necrosis was extensive, but autolysis and débridement were incomplete. Ghostlike outlines and groups of swollen, granular, nonstaining, dead liver cells were still plentiful in various sections (fig. 3*B*). In this case, too, the inflammatory component was striking but not as extensive as in case 3, in which death occurred at a still earlier stage. These 2 cases indicate that the intensity of the inflammatory component is transient, being most severe in the earlier stages, Apparently, the inflammatory changes subside somewhat after autolysis of liver cells has occurred and after the cell debris has been removed. Ordinarily, when sections of liver are seen in cases of hepatitis, autolysis is well advanced or has been completed. Uniquely, in these cases the early stages of destruction were seen, and it appears that swelling of the liver cells,

their detachment from one another and coagulative necrosis precede autolysis. The exact mechanism of the removal of debris is not understood, although because of its rapidity it is presumed to be enzymatic action.[14a] This series of cases would indicate that it is completed by the seventh and tenth days. Generally, many Kupffer cells, as well as mononuclear phagocytes, contained demonstrable but variable amounts of lipochrome pigment. An attempt at regeneration of liver cells was seen in only 2 cases (8 and 9). Proliferation of perilobular bile ducts, however, was observed in several. Ordinarily, in the vast majority of patients who recover, complete regenerative restitution of liver cells is thought to occur, although a sufficiently large number of cases has not been examined to determine this point with finality. The preservation of the reticular framework seems to provide a scaffolding for this reconstruction.[14b]

(*b*) Lymph Nodes: Acute lymphadenitis of a regional type was frequently notable. This was characterized not only by edema, lymphoid hyperplasia and infiltration of lymphocytes and mononuclear phagocytes but occasionally by occurrence of focal areas of necrosis. These areas involved chiefly germinal centers of lymphoid follicles (fig. *2D*) and resembled similar necroses involving centers of malpighian bodies of the spleen.

(*c*) Spleen: In each instance the spleen was enlarged, the weight varying from 211 to 622 Gm. (table). Characteristically in the early stages it was not only enlarged but soft and boggy (cases 3, 6 and 8). Later it became firm and smaller, and still later, after a prolonged course, not only firm but enlarged again (case 10). Histologic studies showed in the early stages of the disease definite splenitis, characterized by the occasional occurrence of focal necrosis or of necrosis involving the central portions of large, hyperplastic malpighian bodies, lymphocytic infiltration of the recticulum of the pulp, and areas of edema in the supporting stroma (fig. *2A*). These changes are variable in severity and occur only in the early stages of the disease. Later, the malpighian bodies become small and compact. The capsule becomes tense and friable in the early stages. Rupture of the splenic capsule occurred with resultant fatal hemoperitoneum in 1 case (3). In another case (8) the capsule was so tense and friable that it was readily lacerated at autopsy in spite of careful manipulation in its removal. Inasmuch as the lesions of splenitis are most marked in the early stages, before the process of cell death and autolysis observed in the liver has occurred or reached its acme, it seems probable that the splenic lesions are due to direct action of the icterogenic agent which is responsible for the characteristic lesions elsewhere (in the liver, the lymph nodes, the testes, and occasionally the heart, the lungs and the brain). To me this explanation seems more

likely than the hypothesis that "the early lymphoid hyperplasia is probably a reaction to products of tissue breakdown in the liver."[14a] Splenic enlargement in the late stages after subsidence of the acute splenic enlargement seen in the first few days of the disease is most probably due to congestion and hyperplasia of the pulp.

(*d*) Testes: Even though variable degrees of arrest of spermatogenesis were noted in the majority of cases, both at early and at late stages, definite orchitis occurred at early stages in a number of cases (fig. 2*B*). The arrest of spermatogenesis may have been due to a number of factors —infection, fever, debilitation, metabolic disturbances subsequent to wounds, and nondisposal of estrogens concomitant with damage of the liver. Testicular changes characterized by arrest of spermatogenesis have been noted quite commonly but not universally by other writers, and it has been assumed to be due to a disturbance in the disposal of estrogens occasioned by the damage of the liver. Orchitis, on the other hand, does occur in the early stages, is representative of one of the systemic lesions of the initial disease and may well be an additional factor promoting early arrest of spermatogenesis.

(*e*) Kidneys: A variable, usually mild, type of cholemic nephrosis occurred in several cases.

(*f*) Brain: No characteristic anatomic lesions were found to account adequately for the neurologic disturbances, which were often fleeting and occasionally profound. In cases 1 and 2 neurologic and mental disturbances were profound, culminating in 1 case with the occurrence of decerebrate rigidity. The most common findings were in the mesencephalon, the brain and the cerebral white matter. These consisted of marked dilatation of the tiny blood vessels, some of which contained recent thrombi, and occasional small perivascular hemorrhages. Mild meningoencephalitis was found in 1 case. It seems clear that physiologic disturbances, coincident possibly with failure of an enzyme system concerned with carbohydrate metabolism, rather than morphologic, in cases of severe hepatic damage are responsible for the neurologic manifestations. One unusual coincidental intracranial finding is worthy of especial comment, namely, an area of internal hemorrhagic pachymeningitis with scarring of the underlying cerebral cortex in a patient who had sustained an immersion blast injury four months previously. Recent bleeding may well have been accentuated by an acute hemorrhagic diathesis consequent to damage of the liver and impaired formation of prothrombin. The intracranial lesion is of great coincidental interest from the point of view of etiology. In the absence of syphilis, alcoholism, recent trauma and other factors commonly associated with occurrence of such a lesion there is the definite suggestion that it may have occurred as the sequel to immersion blast injury. To date there have been reported no instances

of dural and adjacent cortical lesions developing secondary to such a trauma.

(*g*) Gastrointestinal Tract: Phlegmonous inflammation and edema of the gastrointestinal tract were not noted. Such phenomena have been reported when the patient survived for a much longer interval.[14a] Their absence in the cases of the present series, in most of which death occurred early, would indicate that phlegmonous inflammation and edema are sequelae. No gastric lesions were observed such as have been recently alluded to by Knight and Cogswell.[24]

(*h*) Hemorrhagic Phenomena: Of variable degree and occurrence were the small ecchymotic hemorrhages in the epicardium and the mucosa of the renal pelves and beneath the endocardium of the left ventricle (septum and papillary muscles). As previously stated, it is thought that decreased formation of prothrombin secondary to severe damage of the liver is most probably responsible for their occurrence.

(*i*) Lungs: In 2 cases interstitial pneumonitis was shown.

(*j*) Heart: In case 3 there occurred definite myocarditis, which was characterized by infiltrating lymphocytes and mononuclear phagocytes. These were most numerous beneath the endocardium and in the papillary muscles.

SUMMARY

Fatal acute epidemic hepatitis occurred in 10 members of the naval personnel. The age of these patients varied from 19 to 28 years.

Six of the patients who died had been wounded three to four months previously. In this group of previously wounded men the possibility of "homologous serum jaundice" with maximum periods of incubation up to four months could not be excluded. The hepatitis in this group was fulminating and characterized by a clinical course of ten days or less. The classic preicteric phase usually seen in acute epidemic hepatitis was either absent or obscured by other conditions. In 1 case the cephalin cholesterol flocculation test gave a positive result on two occasions one month before the advent of clinical jaundice. The mortality rate in this group was 19 per cent in contrast to the characteristically low mortality rate (0.13 to 0.44 per cent) reported in the literature for cases of epidemic hepatitis.

Inasmuch as 80 per cent of the total number of patients died within from two to ten days after the onset of hepatitis, it was possible to study the lesions at an early stage in their development. This was a much earlier stage than in other outbreaks, in which the disease ran a more protracted course.

24. Knight, W. A., and Cogswell, R. C.: J. A. M. A. **128**:803, 1945.

One patient died on the second day of illness from a spontaneous rupture of the spleen with an ensuing fatal hemoperitoneum.

Consistently, the livers showed changes similar to those of "acute yellow atrophy." At the earliest stage at which the lesions were examined (second day), the liver cells were swollen and detached from one another, and only minimal autolysis had occurred. By the tenth day, however, most of the damaged liver cells had become autolyzed, and the cellular debris had been removed. An accompanying inflammatory component, consisting chiefly of the presence of lymphocytes and monocytes, was most marked in the earlier stages. Gross nodulation was either absent or minimal in the livers of patients who lived ten days or less.

The spleen showed varying degrees of enlargement. In a number of instances necrosis was observed in the germinal centers of the splenic malpighian bodies and regional lymph nodes. Characteristically, the regional lymph nodes were enlarged and spongy and showed lymphadenitis.

Uniformly, arrest of spermatogenesis occurred, which in a majority of the cases in which the lesions were in an early stage was associated with definite orchitis.

Miscellaneous lesions occurred in several cases in which the disease was studied at an early stage. Interstitial pneumonitis was present in 2 instances. A mild type of meningoencephalitis was found in 1 instance and myocarditis in 1 instance.

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CHEMICAL FACTORS AND THEIR ROLE IN INFLAMMATION

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CELLULAR injury involves a radical alteration in the biochemistry of the cell. The consequence is the liberation of various common denominators, which in turn are readily recovered from the exudative fluid bathing the injured cells. The presence of these substances is of aid in explaining the basic pattern of numerous processes that accompany severe injury. Inflammation is essentially a manifestation of severe cellular injury in the tissues of higher animals. The phenomenon of inflammation requires the presence of vascular channels, lymphatic structures and tissue cells besides the emigrating leukocytes and the outpouring of fluid from the circulating blood.

In connection with studies of exudates a crystalline-like nitrogenous substance was isolated. This material is per se capable of explaining reasonably the increased capillary permeability and the migration of leukocytes in acute inflammation. It has no apparent relation to histamine. To it the name "leukotaxine" has been assigned.[1] Another type of material liberated by the injured cells in inflammation is glucose. The surplus sugar produced, probably by deamination of the protein molecule at the site of injury, offers an explanation of the enhancement of diabetic conditions that frequently presents itself with infections.[2] Fundamentally, any injured cell is potentially gluconeogenetic.[3]

I shall not comment further on either leukotaxine or the glucose produced at the site of acute inflammation. Rather I shall devote the rest of this paper to more recent studies on the leukocytosis-promoting factor, on the pattern of injury (necrosin), on the pyrogenic factor (pyrexin) and on a more recently studied leukopenic factor which appears at the site of acute inflammation.[4]

From the Department of Pathology, Duke University School of Medicine.

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1. Menkin, V.: Dynamics of Inflammation, New York, The Macmillan Company, 1940.

2. Menkin, V.: Am. J. Physiol. **134**:517, 1941.

3. Menkin, V.: Am. J. Physiol. **138**:396, 1943.

4. Menkin, V.: (*a*) Am. J. Path. **16**:13, 1940; (*b*) Arch. Path. **30**:363, 1940. (*c*) Menkin, V., and Kadish, M. A.: ibid. **33**:193, 1942. (*d*) Menkin, V.: Am. J. Path. **19**:1021, 1943; (*e*) Arch. Path. **36**:269, 1943; (*f*) Am. J. M. Sc. **208**:290, 1944; (*g*) Arch. Path. **39**:28, 1945; (*h*) **41**:50, 1946.

THE MECHANISM OF LEUKOCYTOSIS WITH INFLAMMATION

Leukotaxine is concerned with the leukocytes migrating locally into an area of acute injury, but it seems to have little to do with regulating the number of circulating white cells.[4a] When introduced intravenously into a rabbit for several successive days it fails to alter appreciably the leukocytic level in the blood stream. This is true likewise in the dog. On the other hand, the absolute number of leukocytes can be readily increased within several hours by injecting into the circulation whole or cell-free exudative material. This observation suggests that exudate contains a leukocytosis-promoting factor, particularly if it is derived from a dog with pleural inflammation and concomitant circulatory leukocytosis. No such rapid effect can be elicited with normal canine blood serum or with various other materials, such as isotonic solution of sodium chloride, broth or even bacteria.

The leukocytosis-promoting factor (abbreviated in the accompanying charts to LPF) is thermolabile, being inactivated at 60 C. It is nondiffusible. These facts have suggested that it is of a protein nature. Fractionation by ammonium sulfate indicates that the active principle is primarily located in the pseudoglobulin fraction, i. e., in the fraction precipitated at one-half saturation with ammonium sulfate.[5] Preliminary studies in collaboration with Dr. Gerald Cooper with the Tiselius cataphoretic apparatus indicate that the leukocytosis-promoting factor seems to be associated with the a_2-globulins of exudates. The active principle is not present in normal serum, but it may be recovered from the blood serum of an animal with a concomitant acute inflammation.[4c] The fact that this factor is liberated into an inflamed area and subsequently penetrates into the blood stream offers a reasonable explanation of the basic mechanism of the leukocytosis that frequently accompanies inflammatory processes. These observations have been made on dogs and on rabbits. Reifenstein and his collaborators have substantiated these studies of exudative material on rabbits.[6] Recently Mattison and I, in as yet unpublished studies, succeeded in obtaining

5. With further purification it has been found essential first to remove the euglobulin fraction of exudate in order to avoid a preliminary leukopenic phase. The final material is then dried by freezing. In this state the leukocytosis-promoting factor soon tends to lose its potency. I have recently found that the material maintains relative potency in vacuo under phosphoric anhydride.[3] Nevertheless, even by this procedure the activity of the material is not sustained for too long. It has been found that activity can be prolonged by maintaining the active material in the presence of ammonium sulfate on ice. The sulfate ions are dialyzed out prior to use of the material. In this way the leukocytosis-promoting factor can be maintained for weeks in the fluid state on ice. After dialysis, drying by freezing can be employed.

6. Reifenstein, G. H.; Ferguson, J. H., and Weiskotten, H. G.: Am. J. Path. **17**:233, 1941.

similar results in guinea pigs (fig. 1). This may render the latter a convenient test species in which to assay various fractions of the leukocytosis-promoting factor. These studies are being pursued further.

Has the leukocytosis-promoting factor any effect on the growth of cells in the bone marrow? The observations indicate that one to two days after it has been injected intravascularly into a dog, marked hyperplasia occurs in the marrow. The tissue becomes replaced with actively growing granulocytic elements and also with megakaryocytes.[4d] The findings warrant the conclusion that the leukocytosis-promoting factor favors hyperplasia both of granulocytes and of megakaryocytes in the marrow, presumably with immature polymorphonuclear leukocytes being simultaneously discharged into the circulation, causing

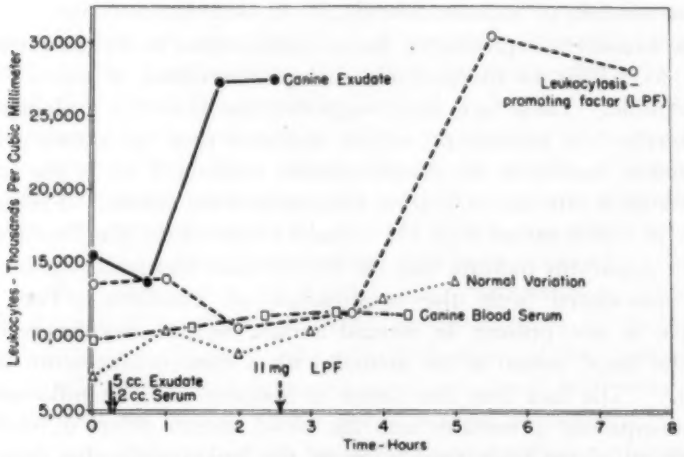


Fig. 1.—Effect of the leukocytosis-promoting factor on the number of the circulating leukocytes of the guinea pig. Canine exudative material when introduced into the peritoneal cavity of the guinea pig induces a sharp increase in the white cells. Identical results have been obtained with 11 mg. of the leukocytosis-promoting factor (LPF). No appreciable effect is observed after the introduction of blood serum. The leukocytosis-promoting factor can likewise be injected subcutaneously.

thus the leukocytosis that frequently accompanies inflammation. The clinical implications of such studies are obvious. The leukocytosis-promoting factor (canine) has been successfully injected intravenously into 10 human subjects. The material is both innocuous and active in amounts varying from 18 to 231 mg. This fact opens definite, and probably clinical, approaches to the general problem (figs. 2 and 3). In preliminary studies, to be reported later, it has been found that the leukocytosis-promoting factor seems to raise the white cell count of a leukopenic patient. One injection of 77 mm. of the material has raised the count from about 2,000 cells per cubic millimeter to over 4,000. The

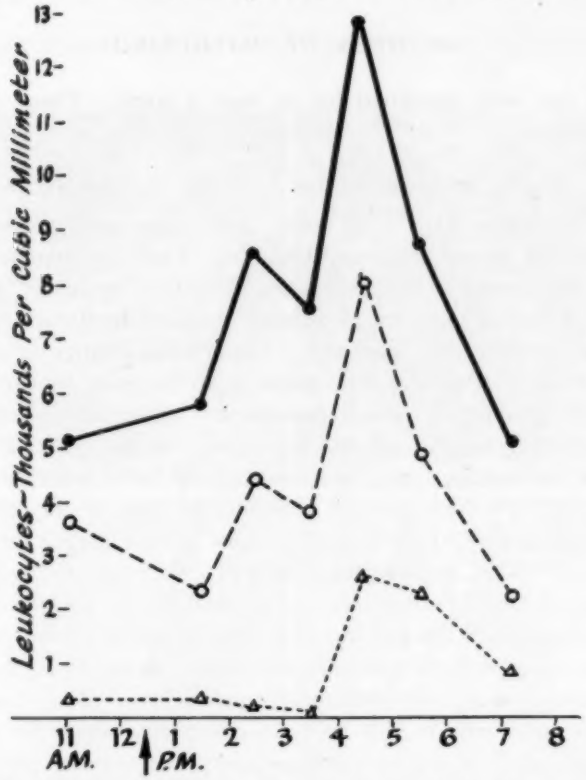


Fig. 2.—Effect of the leukocytosis-promoting factor derived from canine exudative material on the number of circulating leukocytes of a human being. The subject, a Negro 41 years of age, received intravenously 127 mg. of the leukocytosis-promoting factor. (An arrow indicates the time of injection.) This promptly produced a rise in the number of circulating leukocytes (——). The rise was largely due to augmentation of the polymorphonuclear leukocytes (- - - -), which is reflected by an increase in the number of immature neutrophils (one lobe, immature leukocytes). This clinical study is being conducted in collaboration with Dr. E. Ulled and Dr. E. G. Goodman.

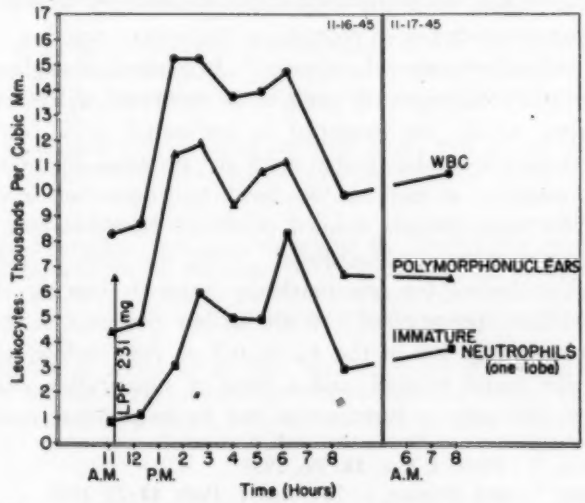


Fig. 3.—Effect of the injection of 231 mg. of the leukocytosis-promoting factor on the circulating leukocytes of a youth aged 19. Note the rapid rise in the number of white cells. This is primarily due to immature polymorphonuclear leukocytes discharged into the circulation.

new level has been sustained for at least a week. These studies are being continued.

THE BASIC MECHANISM OF INJURY IN INFLAMMATION

Close scrutiny reveals a fairly well delineated pattern in the development of an inflammatory reaction. This, for instance, involves the four fundamental cardinal signs described originally by Celsus, as well as a loss of function, as pointed out later by John Hunter. To these basic features one may add a biochemical change in the normal protein metabolism of the cell, namely, an increase in proteolysis or a rise in the products of protein breakdown. The fundamental pattern, as just outlined, may be altered depending on the chemical nature of the irritant and on the interrelationship of the latter with the particular tissue of the host. The precise anatomic location of the affected part may also be a factor to be considered. But by and large a basic reaction of injury persists throughout the course of inflammation.

Is there any conditioning factor to account for the pattern of injury in acute inflammation? The exudate per se when injected into normal tissue will induce an edematous reaction sufficiently intense to be accompanied by lymphatic blockade, an evidence of severe injury.[7] When the exudative material is analyzed, it has been observed that only the euglobulin fraction can elicit a marked inflammatory reaction in the skin of a rabbit.[4e] Further purification has revealed that an injurious factor is either located in the euglobulin fraction of exudate or else closely associated with that particular protein fraction, for neither the pseudoglobulin nor the albumin fraction of exudate induces any appreciable injurious effect.

This euglobulin fraction has of late been dissociated from a pyrogenic and a leukopenic factor, each of which had originally been found in close association with the euglobulin fraction of exudate.[4e] This injurious factor which per se reproduces the severe reaction of an acute inflammation has been termed necrosin.[4e] In general, though not always, it has been found that necrosin tends to be recovered more readily if the exudate from which the material is extracted is at an acid p_H. Originally it had been shown that with the progress in intensity of an acute inflammation a rise in the local hydrogen ion concentration occurs.[8] The local acidosis seemed primarily referable to a glycolytic process causing lactic acid acidosis. With the rise in acidity polymorphonuclear leukocytes are markedly injured, leaving the macrophages essentially unimpaired. With further progress in the reaction and a corresponding fall in the p_H to 6.5 or even below, all types of leukocytes are found injured, and a state of suppuration ensues. Pus formation is virtually a function of the hydrogen ion concentration.

7. Menkin, V.: Physiol. Rev. **18**:366, 1938.
8. Menkin, V., and Warner, C. R.: Am. J. Path. **13**:25, 1937.

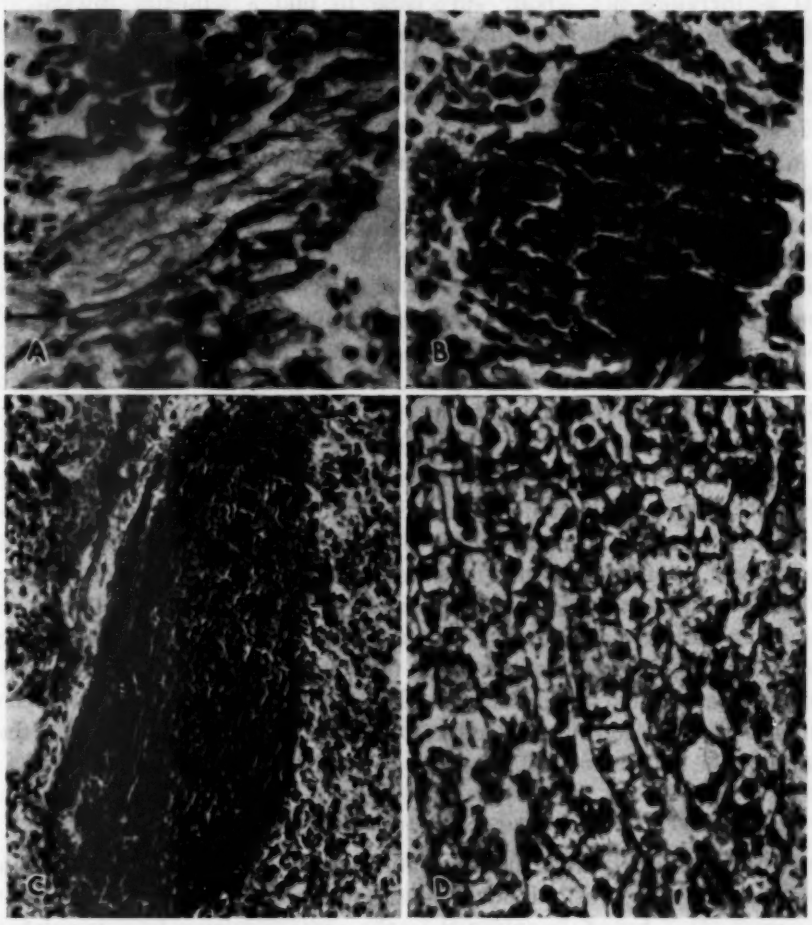


Fig. 4.—*A*, acute inflammatory reaction observed one day after necrosin had been injected into the skin of the abdomen of a rabbit. Note the occlusion of a lymphatic vessel by fibrinous plugs. This is evidence of the severe injury induced by necrosin. × 445.

B, marked reaction evoked within seventeen hours after 0.5 cc. of a suspension of necrosin was injected into the abdominal skin of a rabbit. Microscopic examination revealed occlusion of lymphatic vessels, as shown in *A*. × 485.

C, severe local inflammation induced by 0.5 cc. of a necrosin preparation injected into the skin of a rabbit. Seventeen hours after the injection the area was excised, and subsequent microscopic examination revealed not only occluded lymphatics but blood vessels showing strands of fibrin originating apparently from the endothelial lining. This probably can be considered to be an initial stage of the formation of a thrombus. × 225.

D, denudation of cytoplasm of liver cells. Dog 3D received six intravenous injections of necrosin within a period of three weeks. The animal was then killed. The cytoplasm of the individual liver cell, as shown, seems to be denuded of its content. This appearance of the liver has been found to be referable to abundant deposition of glycogen. × 485.

It is therefore not wholly surprising to find a tendency toward an increase in necrosin with the rise in hydrogen ion concentration in an acutely inflamed area. In this way it is conceivable that the greater formation of necrosin may further the reaction of injury with the increase in acidity.

The degree of injury in inflammation may be conveniently gaged by the development of lymphatic blockade. The lymphatic vessels become plugged with fibrin. Necrosin characteristically induces such a state of affairs (fig. 4 *A* and *B*). The pseudoglobulin and albumin fractions when introduced into tissue leave the lymphatic structures unaltered. In a tissue area in which necrosin has been injected, small vascular channels are found with damage of the endothelial lining (fig. 4 *C*). One of the earliest manifestations of the effect of necrosin injected into the abdominal skin of a rabbit is swelling of the collageneous bundles.

Necrosin is not present in normal blood serum, but it may be recovered to some extent from the serum of an animal with a concomitant acute inflammation. This fact suggests that necrosin is absorbed from the site of an acute inflammation into the circulating blood. Perhaps the fact that necrosin is present in the blood stream of animals with acute inflammation may be of significance in reorienting some present day notions concerning the role of foci of infection in lesions of organs situated at a distance. For this reason, studies have been undertaken to determine the effect of necrosin injected directly into the circulation.

THE EFFECT OF NECROSIN INJECTED INTO THE CIRCULATION

When injected into the circulation of a dog, a single dose of a suspension of necrosin induces most frequently some sort of hepatic injury. This may be manifested in the gross specimen by a tasselated appearance of whitish areas or streaks, which vary considerably in extent. Microscopic examination may reveal scattered foci of disintegrated cells containing a curious granular stippling, which fails to take the iron stain. It is conceivable that this represents nuclear debris. Sometimes the areas of injury reveal vacuolated cells with interspersed foci of leukocytic infiltration. More recently studies have been undertaken to determine what effect necrosin may have on the liver when repeatedly injected into the circulation. Here again injury or alteration of the organ seems to be a frequent feature, although the character of the change seems to vary from animal to animal. Whether this depends wholly on dosage and on the number of injections is not as yet settled. For instance, following two injections of necrosin considerable fatty degeneration has been encountered throughout the parenchyma. On the other hand, six intravascular injections of the material made into

a dog over a period of three weeks induced a curious evacuation of the cytoplasmic constituents in the liver, leaving a bare framework (fig. 4 *D*). The empty spaces have sometimes failed to take the fat stain, but the glycogen present within the cells is so abundant as to leave little doubt that the microscopic appearance of the tissue seems primarily referable to large amounts of glycogen. The animals were starved for about one day prior to being killed, rendering it doubtful that the presence of enormous deposits of glycogen is referable to ingestion of large amounts of carbohydrates. Furthermore, control animals have failed to reveal any such deposits. Finally, when necrosin is administered intravascularly for longer intervals—for example, about two months—not only does there seem to be less deposition of glycogen but the latter appears to be heterogeneously distributed throughout the organ. The failure of the material to be homogeneously deposited in the liver cord suggests a mechanism other than mere ingestion of carbohydrate. It is perhaps conceivable that the formation of glycogen is referable in part to deamination of protein as a result of extensive hepatic cellular injury. These studies are being pursued further.

The kidney at times shows, following a single injection of necrosin, moderate vacuolation of the lining tubular cells, as well as foci of interspersed leukocytic infiltration. Following numerous injections of the material, a peculiar colloid-like material has been found within the capsular space of some of the glomeruli. The liver and quite often the kidneys are the organs most frequently involved after injections of necrosin. Occasionally, though not constantly, a condition of bilateral hydrothorax has been encountered, as well as small hemorrhages throughout the length of the gastrointestinal tract.

In brief, these studies, which are still in progress, at least suggest the significance of a toxic material elaborated by injured cells at the site of an acute inflammation. The absorption of such a substance may have definite repercussions on some of the visceral organs, notably the liver. These facts have to be borne in mind in the further study of the organism as a whole when one of its parts is undergoing a severe inflammatory process.

Smith and Smith [9] have recently described a toxic material in the euglobulin fraction of menstrual blood. Not only have they confirmed the presence of necrosin in exudative material but they also have advanced evidence indicating that necrosin and the toxic material in menstrual blood are identical in nature. This fact is not wholly surprising, for menstrual blood contains, besides blood, debris of cellular injury derived from the damaged endometrium.

9. Smith, O. W., and Smith, G. U. S.: Proc. Soc. Exper. Biol. & Med. **59**:116, 1945.

Earlier studies indicated that necrosin manifests proteolytic activity. These studies have been substantiated further by Dr. Frederick Bernheim and me. These observations will be reported in detail elsewhere.

THE MECHANISM OF FEVER WITH INFLAMMATION

In the early studies on the necrosin present in inflammatory exudate, it had been observed that the euglobulin fraction of exudate, besides inducing local cutaneous injury, caused when injected intravascularly into dogs [4e] a concomitant rise of temperature and transitory leukopenia. These findings suggested further studies to determine whether the fever was referable to the necrosin or to some other substance present in exudate.

Under normal circumstances the dog's temperature hardly fluctuates during a period of about six hours. This is also seen when either the albumin of the pseudoglobulin fraction of exudate (leukocytosis-promoting factor) is introduced into the circulation. The euglobulin fraction of normal blood serum is also ineffective as far as eliciting a rise in temperature is concerned.[10] On the other hand, when the whole euglobulin fraction of exudative material is injected intravascularly a rapid rise in temperature occurs which in the series studied averaged about 3 F.[10]

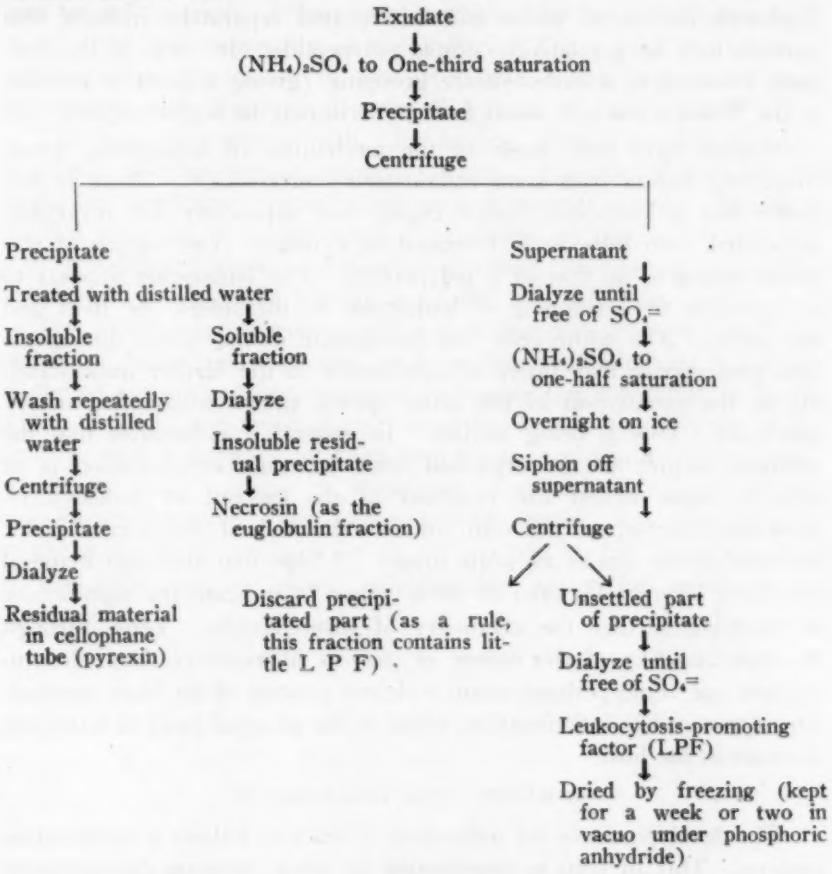
These studies have been repeated on the rabbit as a convenient test animal.[11] A rabbit's temperature during a period of about six hours fluctuates maximally on the average about 0.6 F. unless there is extreme hot weather, in which the temperature of the animal may rise about 1 F. Saline solution, the euglobulin fraction of normal canine or human blood serum and the leukocytosis-promoting factor of exudate are all incapable of inducing an appreciable rise in body temperature. When the exudate obtained from the pleural cavity of a dog into which turpentine was previously injected is introduced into the circulation of a rabbit, a rapid rise in the animal's temperature frequently occurs. The average increase is about 2.3 F. This significant rise is duplicated only when the euglobulin fraction of the exudate is used, the average increase being about 2.5 F. Neither blood serum nor its euglobulin fraction evokes any appreciable fever; at least the fever does not rise to the same level as that elicited by the euglobulin fraction of exudate.

In the early studies it was noted that the euglobulin fraction maintained itself as a suspension in the presence of electrolytes. This seemed to be contrary to the accepted notion of euglobulins. It appeared at first as if one were dealing with an atypical euglobulin.[11]

Further studies, however, soon showed that one was really dealing with two different substances. One of these was the euglobulin fraction

10. Menkin, V.: Proc. Soc. Exper. Biol. & Med. **54**:184, 1943.
11. Menkin, V.: Federation Proc. **3**:32, 1944.

proper which proved toxic when injected into the skin of a rabbit. This was necrosin. Necrosin thus far has failed to be dissociated from the true euglobulin fraction of exudate. But in the same fraction there exists another fraction incapable of entering into solution in the presence of electrolytes. This fraction, which can often be dissociated by differential solubility from necrosin or the euglobulin fraction of exudate, tends to be extremely pyrogenic in contrast to purified necrosin. The latter is scarcely capable of inducing fever. In brief, the scheme of the recovery of necrosin and the fever factor, termed pyrexin, and the modified method by which the leukocytosis-promoting factor may be extracted from a sample of exudate can perhaps be conveniently outlined as follows:



The fact that pyrexin is often, though not always, recovered from exudates that are at an acid *p*H to start suggests an explanation for the primary mechanism of the fever that occurs with inflammation. There is some evidence that this fraction acts on the heat-regulating

center in the hypothalamic region, for pentobarbital sodium and antipyretic drugs inhibit the full biologic activity of this substance. The latter substances are supposed to inhibit the action of the heat-regulating centers in the central nervous system. There is also some evidence that pyrexin is eliminated at least in part in the urine. A dog with an acute pleural inflammation gradually excretes this pyrogenic factor in the urine.[4g]

Pyrexin is heat stable. Boiling fails to inactivate it. When tested with ninhydrin, the reaction is positive. In the biuret test the reaction is positive but only in minute trace. Contrary to earlier observations, further studies have indicated that it gives a positive reaction in the Molisch test. Observations made in collaboration with Dr. Frederick Bernheim, which will be reported separately, indicate that pyrexin may be a relatively simple polypeptide. In view of the constant presence of a carbohydrate grouping (giving a positive reaction in the Molisch test), it seems as if pyrexin may be a glycopeptide.

Studies have been made of the mechanism of leukopenia, which frequently occurs with some inflammatory processes.[4h] There is evidence that a leukopenic factor closely but apparently not invariably associated with pyrexin is liberated in exudate. The nature of this factor seems to be that of a polypeptide. The leukopenia appears to be referable to a trapping of leukocytes in the lungs, the liver and the spleen. The white cells that accumulate in the spleen during the leukopenic phase may prove of significance in the further understanding of the mechanism of the acute splenic tumor with inflammatory processes. This is being studied. In general it is possible that the ultimate picture in the organism with an acute inflammation is at least to some extent the resultant of the amount of leukocytosis-promoting factor, of necrosin, of pyrexin and of leukopenic factor liberated at the site of an acute injury. I hope that sufficient material has been brought forward in these pages to indicate the significance of studying further the chemistry of injured cells. Thus, through an understanding of the nature of various liberated common denominators, one could perhaps attain a clearer concept of the basic mechanisms concerned in inflammation, which is the physical basis of infectious diseases in the host.

SUMMARY AND CONCLUSIONS

The development of the inflammatory reaction follows a fundamental pattern. This in turn is conditioned by some common denominators that can be extracted from the exudative material. For instance, the increase of capillary permeability and the migration of polymorphonuclear leukocytes are primarily referable to leukotaxine, presumably from injured cells. Glucose is likewise produced by damaged cells.

The leukocytosis frequently accompanying inflammatory processes is apparently due to a protein in the pseudoglobulin fraction of exudate. This substance, besides inducing a discharge of immature granulocytes from the bone marrow, also causes a marked hyperplastic reaction of these elements and of megakaryocytes in the marrow. The leukocytosis-promoting factor (LPF) affects the circulating leukocytes of dogs and of guinea pigs. The canine leukocytosis-promoting factor is both innocuous and active in human beings. When injected into the blood of man it induces a rise in circulating leukocytes ranging from 80 to 150 per cent.

The pattern of injury causing inflammation seems primarily referable to a toxic euglobulin liberated by injured cells. This factor has been termed necrosin. When intravascularly injected it induces injury of the liver and frequently of the kidney. The injury of the liver varies from a denudation of the cytoplasm of the hepatic cell and replacement with abundant glycogen to a large deposition of fat.

The fever that occurs with inflammation seems referable to what is possibly a glycopeptide, termed pyrexin. Pyrexin appears to act on the heat-regulating centers of the central nervous system. Although purified necrosin is nonpyrogenic, incubation of this substance frequently yields a pyrogenic substance, suggesting that pyrexin is possibly the product of enzymatic activity associated with necrosin.

The leukopenia often observed with inflammation seems referable, at least in numerous instances, to a leukopenic factor which can be recovered from exudative material, particularly if the latter is at an acid p_H. The leukopenic factor is often in close association with pyrexin, and it appears to be a heat-stable polypeptide. Its action appears to be a trapping of leukocytes in the alveolar walls of the lung, in the sinusoids of the liver and in the spleen. The cells retained in the spleen may perhaps be of aid in the further understanding of the acute splenic tumor accompanying numerous inflammatory processes.

ADENOCARCINOMA OF THE URACHUS INVOLVING THE URINARY BLADDER

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THE paucity of reports of adenocarcinoma of the bladder arising from the urachus is rather striking, since neither tumors of the bladder nor urachus rests are particularly rare. Cases of tumor of the bladder constitute 3 per cent of all urologic cases (Verhoogen [1]), a figure which is in close agreement with the 4 per cent determined by Young [2] in an analysis of 12,500 cases.

In regard to urachus rests, Wutz [3] found 24 cysts in 74 cases, while Morse [4] was able to determine the existence of 13 cysts or patent urachal tubules in 21 consecutive autopsies. Begg [5] stated that careful dissection and histologic search would reveal urachal rests or cysts in the majority of the cases examined, a fact which appears to be substantiated by Saphir and Kurland,[6] who demonstrated the presence of typical tubular structures in the vault of the bladder in the region of the ligamentum umbilicale mediale in 9 of 10 bladders.

Nothwithstanding this frequency, Begg [5] in 1931 succeeded in collecting only 19 cases of colloid adenocarcinoma from among 29 assorted cases of urachal tumor involving the bladder wall and the space immediately above it. This total did not include the case of Lane and Morson,[7] which appeared in 1930. Begg [8] added an additional case in 1936,

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1. Verhoogen, J., in Pousson, A., and Desmons, E.: Encyclopédie française d'urologie, Paris, G. Doin, 1921, vol. 4, p. 225.

2. Young, H.: Practice of Urology, Philadelphia, W. B. Saunders Company, 1926.

3. Wutz, J. B.: Virchows Arch. f. path. Anat. **92**:387, 1883; cited by Rankin and Parker.[12]

4. Morse, H., cited by Rankin and Parker.[12]

5. Begg, R. C.: Brit. J. Surg. **18**:422, 1931.

6. Saphir, O., and Kurland, S. K.: Urol. & Cutan. Rev. **43**:709, 1939.

7. Lane, C. R., and Morson, A. C.: Brit. J. Urol. **2**:271, 1930.

8. Begg, R. C.: Brit. J. Surg. **23**:769, 1936.

while in the same year Ferrier, Craig and Foord[9] reported 2 cases. Saphir and Kurland increased the total to 24 by publishing 1 case in 1939. Ash[10] found only 2 cases of adenocarcinoma which he thought might be derived from urachus rests, out of a total of 2,000 cases of tumor of the bladder which were registered at the Army Medical Museum.

Although urachal tumors are rare, it is important that each one that occurs should be differentiated from other tumors that may occur in the vault of the bladder, since the accepted therapy of papillary tumors, such as fulguration or radium implantation, is valueless, whereas surgical removal of the young lesion offers some hope.[11] The fundamental study of urachal tumors has been furnished by Begg,[5] from whose article the following details are abstracted, since his paper appeared in an otherwise not readily accessible journal.

ORIGIN AND DEVELOPMENT OF THE URACHUS

The derivation and the development of the urachus are described in most standard embryologic texts, to which the reader is directed. For the purpose of the present paper, the following brief description will serve to orient the subject.

The primitive hindgut in the early fetus is the anlage of the rectum, the upper part of the bladder and the urachus. This cavity, the cloaca, is lined by a single layer of cuboidal cells. With the formation of the urorectal septum, the cloaca becomes divided into the bladder and the urachus on one side and the rectum on the other. The cuboidal epithelium accordingly undergoes differentiation into the transitional epithelium of the bladder and the cylindric intestinal epithelium of the rectum. The epithelium of the urachus, however, belonging to an organ of no particular function, undergoes no specialization, in contrast to that of the rectum and the bladder, but remains as a primitive layer retaining all of the potentialities of primitive cells. This retention of potency is the key to the understanding of the various types of tumor of the urachus. Complete but ill regulated development toward glandular or transitional epithelium may overstep all bounds and give rise to colloid adenocarcinoma, on the one hand, or squamous cell epithelioma, on the other. Both types were described in a single case by Rankin and Parker[12]; usually,

9. Ferrier, P. A.; Craig, L. G., and Foord, A. G.: Urol. & Cutan. Rev. **40**: 457, 1936.

10. Ash, J. E., cited by Fleischman, A. G., and Mauritz, E. L.: J. Urol. **47**:658, 1942.

11. Lowsley, O. S., and Kirwin, T. J.: Clinical Urology, Baltimore, Williams & Wilkins Company, 1944, vol. 2, p. 1059.

12. Rankin, F. W., and Parker, B.: Surg., Gynec. & Obst. **42**:19, 1926.

however, the endodermal impulse predominates, with the resulting formation of adenoma and eventually of adenocarcinoma.

CLASSIFICATION OF URACHAL TUMORS AND PATHOLOGIC ANATOMY OF THE URACHUS

The urachus measures 5 to 6 cm. in length and may be subdivided into various sections: (1) supravesical where it is entirely above the bladder; (2) intramural where it lies within the muscle wall, and (3) intramucosal where its lumen is in direct continuity with the lumen of the bladder; this continuity occurs in about 33 per cent of the cases. The centimeter which penetrates the wall is the most important from the pathologic point of view, for it is usually at the upper part of this portion or in the lower end of the extravesical section that new growth originates. On the basis of the foregoing subdivision the tumors may be classified as intramucosal, intramural or supravesical.

Most of the specimens described fall into one of two varieties. The tumors of the first group possess typical characteristics. The upper part is encapsulated and extends well into the space of Retzius, while the lower end, which is in the bladder wall, has no definite capsule, the acini lying in direct contact with the muscular tissue. The majority penetrate the mucosa, but the length of the symptomless urinary history, combined with their large size and the presence of calcification in the capsule and the stroma, lead to the conclusion that they exist for a considerable length of time as simple tumors and only late in their course take on malignant characteristics.

The neoplasms of the second group apparently arise from adenomatous structures of the urachus and become cancerous at an early stage. This type is almost entirely within the wall of the bladder, and there is no capsule. The tumor is usually found by cystoscopy or at postmortem examination, and masses are usually not palpable.

In the first group, to which our specimen belongs, the growths range in size from that of a hazelnut (Kielleuthner [13]) to that of an adult head (Pendl [14]). There are usually two components, a supravesical cystic and an intramural solid portion. The capsule of the cyst is in direct continuity with the muscular and adventitial wall of the bladder below. The cells of the solid portion invade the musculature of the bladder directly.

The consistency of the mass is usually fluctuant, since it is mainly composed of multiloculated spaces separated by thin septums and containing a clear gelatinous viscid fluid. The upper part of the tumor lies

13. Kielleuthner, L.: Ztschr. f. Urol. **23**:519, 1929.
14. Pendl, F.: Beitr. z. klin. Chir. **19**:681, 1914.

between the transversalis fascia and the peritoneum of the anterior abdominal wall near the midline. Usually it is adherent to the peritoneum, and occasionally it breaks through this layer, forming adhesions with the abdominal contents. Frequently the tumor may not be in the midline but on the right or the left because of pull by the lateral umbilical ligaments. The upper end may be pulled laterally and downward so that it takes a course from the apex of the bladder upward and outward to the right or to the left.

The capsule of the upper portion of the tumor is fairly definite. Of variable thickness, it may be composed of fibromuscular tissue or old hyalinized connective tissue showing calcareous deposits. There are usually vestiges of acini on the inner surface, evidence of the fact that the capsule is merely compressed tumor.

The stroma consists of fibrous bands of varying thickness which converge in the center. It may show hyalinization and calcification. It encloses spaces varying in magnitude from microscopic ones to huge cysts.

Microscopically, the surface of the tumor, the cysts and the acini are lined by cylindric cells showing various phases of mucin production or mucinous degeneration. They are frequently pleomorphic and frankly carcinomatous and reproduce by amitotic division. While the general appearance of the tumor bears a strong resemblance to rectal cancer, definite differences exist which permit differentiation between rectal and apical cancer. Rectal cancer as a rule produces a more developed and permanent type of granular cell which holds its form longer and is more stable than that of a tumor of the urachus. In the latter, so great is the production of mucus and so rapid the breakdown of the cells that the formed elements occur over a very limited area. The cell goes through its cycle of mucin production and is soon destroyed by its own activity. It is crushed out of existence before it can take part in the fantastic riot and vicious activity of its fellows.

CLINICAL HISTORY

Usually complaints due to the growth of the tumor are elicited before any disturbance in micturition ensues. Owing to interference with the action of the urachus, there is some hesitancy in starting the stream, and there is mild frequency. The first complaint is usually abdominal discomfort and tenderness on palpation in the suprapubic region, where a mass may be seen or felt. Often the first symptom is hematuria with frequency which, owing to inflammation, is usually associated with pain on micturition. Later, pieces of tumor or a glairy mucoid substance may be found in the urine. Inflammatory phenomena may mask the hematuria, since, as in all cases of cancer of the bladder, infection is likely to set in early.

DIFFERENTIAL DIAGNOSIS

Because of the suprapubic mass, one should consider neoplasms of the omphalomesenteric duct, echinococcic cysts, abscess in the space of Retzius, lipoma and cyst arising within the abdominal cavity.

CYSTOSCOPIC APPEARANCE

Tumor of the urachus may be present merely as a protrusion or swelling of the apex of the bladder, giving the impression that something is pressing from the outside. There may be merely what appears to be a flat epithelioma. In other cases there may be a funnel-shaped retraction of the apex of the bladder with a ring of tumor around it. In others, there may be papillary or polypoid masses projecting into the bladder. Occasionally gelatinous fluid may be passing into the bladder. Induration is usually present.

AGE INCIDENCE

In Beggs's series no tumor occurring in a patient younger than 29 was observed, and the majority appeared after middle life. In the same series, 14 tumors occurred in males and only 4 in females.

TREATMENT

Metastases are rare, but they are relatively frequent after surgical intervention. From this it is apparent that any operation must be radical. Metastases following operation occur in the space of Retzius; therefore, the operative specimen should include the umbilicus, a wedge-shaped block of the transversalis fascia, the peritoneum and at least the upper half of the bladder.

PROGNOSIS

There is no evidence concerning the cancerous potentiality of the untreated tumor. The prolonged history in cases of cancer indicates that cancer has superimposed itself on a noncancerous tumor rather than that the tumor is of relatively low malignancy. None of the patients observed lived more than two and a half years after operation. Immediate operative results are good.

REPORT OF A CASE

A white man, aged 26, in 1940 complained of pain in the lower right quadrant of the abdomen suggesting appendicitis. In March 1943 he began to pass bloody urine which contained a glairy mucoid exudate. He experienced intermittent episodes of painless hematuria for four to five months, after which stranguria, urgency and daily hematuria began. In spite of this, it was not until May 1944 that he was admitted to a station hospital. On cystoscopy, a tumor about the size of a small apple, which had bits of necrotic tissue and calcareous plaques attached to it, was seen on the posterodextrolateral wall of the bladder, allegedly 10 cm. above the

right ureteral orifice. A cystogram showed an irregular filling defect and calcification in the right upper third of the bladder wall. The diagnosis was probable papillary carcinoma of the bladder.

The patient was transferred to a general military hospital in June 1944, over four years after the onset of symptoms. A grapefruit-sized mass was palpable in the suprapubic region. This extended to within two and a half fingerbreadths of the umbilicus and was situated somewhat to the right of the midline. The mass was exquisitely tender to palpation, and there was rebound tenderness. On rectal examination a doughy mass the size of a tennis ball was palpable above and to the right of the prostate. Urinalysis showed large numbers of red blood cells and pus cells. Blood counts revealed moderate anemia and some increase in leukocytes.

Intravenous pyelography and cystography showed a flat depression of the superior portion of the bladder with a slight convexity, which was attributed to pressure from a mass external to the bladder. There was some dilatation of the upper portion of the right ureter and the renal pelvis, indicative of obstruction. The belief was entertained that the patient had an old appendical abscess involving the lower right quadrant of the abdomen and the pelvis, which caused the bladder defects.

Cystoscopy substantiated the diagnosis of tumor of the bladder, however, since a sessile cauliflower-like mass, measuring 3.5 to 4.0 cm. in diameter and projecting 1.5 cm. into the lumen, could be visualized in the dome of the bladder near the insertion of the urachus. A specimen of urine collected at that time contained a large amount of mucoid material in which large numbers of pleomorphic cells with irregular-shaped nuclei were present. These were diagnosed as cancer cells, type undetermined.

On operation a grapefruit-sized tense, fluctuant, cystic tumor was found firmly attached to the anterior abdominal wall in the space of Retzius and between the parietal peritoneum and the transversalis fascia. The mass was firmly adherent to the dome of the bladder, where its inferior pole formed an apple-sized firm mass in the bladder wall. A circumferential incision was made in the normal portion of the vault of the bladder wall outside of the intravesical tumor. The cyst was stripped away from the abdominal wall, but unfortunately it was incised, and a large amount of hemorrhagic mucinous material escaped. The posterior portion of the cyst wall could not be removed and was left in situ.

The cystotomy wound healed slowly but gradually closed over. The patient was able to void spontaneously. He became afebrile, gained weight and was quite comfortable. Sigmoidoscopic examination was performed about one month after the operation, and no neoplastic alterations of the mucosa of the rectum or the sigmoid were noted. There was no bloody discharge, nor could any relationship between the fundus of the bladder and the sigmoid or the rectum be demonstrated. Four months after admission the patient was transferred to another general hospital for high voltage roentgen therapy.

At that time the suprapubic wound was almost completely healed. There was a firm, smooth-surfaced, slightly tender mass approximately the size of a lemon in the left lower quadrant of the abdomen above and parallel to the inguinal ligament. The impression was that there were palpable nodules along the anterior margin of the liver. There was no generalized lymphadenopathy. Cystoscopy revealed no deformity or infiltration anywhere. Anteriorly the suprapubic scar could be seen. It was somewhat indurated, and there was some suggestion of recurrence, because of the presence of a small nodule measuring 3 mm. in diameter.

Revisualization several weeks later proved that a yellow lesion was present, which was too small for biopsy, situated in the distal portion of the old suprapubic scar.

Intravenous cystography showed some flattening of the left superior quadrant of the bladder associated with some lateral displacement of the left ureter near the margin of the bladder. Retrograde pyelography showed that both ureters were quite large and also showed the lateral displacement of the left ureter. The belief was expressed that a mass might be present which was causing this displacement. No abnormalities of the contour of the bladder were evidenced on opaque and air cystography.

Repeated roentgenologic examination of the skeleton and the lungs failed to demonstrate any metastatic involvement of these organs.

The patient's condition at the time of writing (June 1945) is quite satisfactory. He is ambulatory, weighs 160 pounds (72.5 Kg.) and has no genitourinary complaints. Because of the presence of the mass in the left lower quadrant of the abdomen and the evidence of displacement of the left ureter, local recurrence or metastases is suspected.

Pathologic Report.—(*a*) Gross Appearance of Specimen: The operative specimen consists of the vault of the bladder comprising a grapefruit-sized supravesical cystic structure and an apple-sized solid intramural portion. The intramucosal aspect (fig. 1) measures approximately 4.5 cm. in diameter. The central portion consists of a nodular, raspberry-like, red soft polypoid tumor which projects above the surface. Many small crypt openings, from which well large amounts of mucoid substance, may be seen between the nodules. Between the crypts the surface of the nodule is lined by discolored, ulcerated mucosa. Other portions of the tumor possess a villous, friable, gelatinous appearance. A smooth, pale, occasionally indurated seam of bladder mucosa measuring 0.5 cm. in width surrounds this central tumor. The wall of the supravesical cyst merges with the adventitia and the muscle coat of the bladder. The cyst wall measures approximately 3 to 4 mm. in thickness. Its external surface is smooth and glistening, while its internal aspect is somewhat rough and nodular and appears to be lined by accumulations of nonadherent, crumbling gelatinous material. The cyst is not entire, a wedge-shaped segment of wall from the posterior aspect being absent.

The intracystic part of the tumor is composed of a papillary, lobular, friable, hemorrhagic, necrotic, gelatinous mass which forms a raised branching stalk that projects into the lumen of the cyst. In the center of this stalk one notes a white-gray, rather firm fibrous plaque, in the center of which is a small circular opening. Serial sagittal sections of the tumor (fig. 2) disclose almost complete honeycombing throughout. Large multiloculated spaces are distended with clear, white, gelatinous material separated by irregularly shaped and sized fibrous septums. On one side the muscle coat is completely replaced by the colloid tumor, whereas on the other, the smooth muscle of the bladder is markedly thickened, firm and hyperplastic, although infiltrated to some extent by tumor. Coursing perpendicularly, although inclined somewhat toward the right, is the urachus, the thick fibrous walls of which are quite sharply defined; from its outer surface radiate septums forming the connective tissue stroma of the mass. The lumen contains an elongated calcified plug, which is rather firmly attached to the left side of the wall. Between the wall and the plug there is a definite space filled with mucinous debris. On serial sections this tubule can be seen to communicate between the urinary bladder and the lumen of the supravesical cyst, the opening of which was noted earlier in this paragraph. Diffuse areas of hemorrhage are seen throughout.

(*b*) Microscopic Appearance: Sections of the intramucosal portion of the tumor reveal the usual transitional epithelium of the bladder, which invaginates rather sharply into a crypt where it forms tubular and branching tubular mucous glands (figs. 4 and 5). These are lined by a rather regular row of columnar epithelium, in

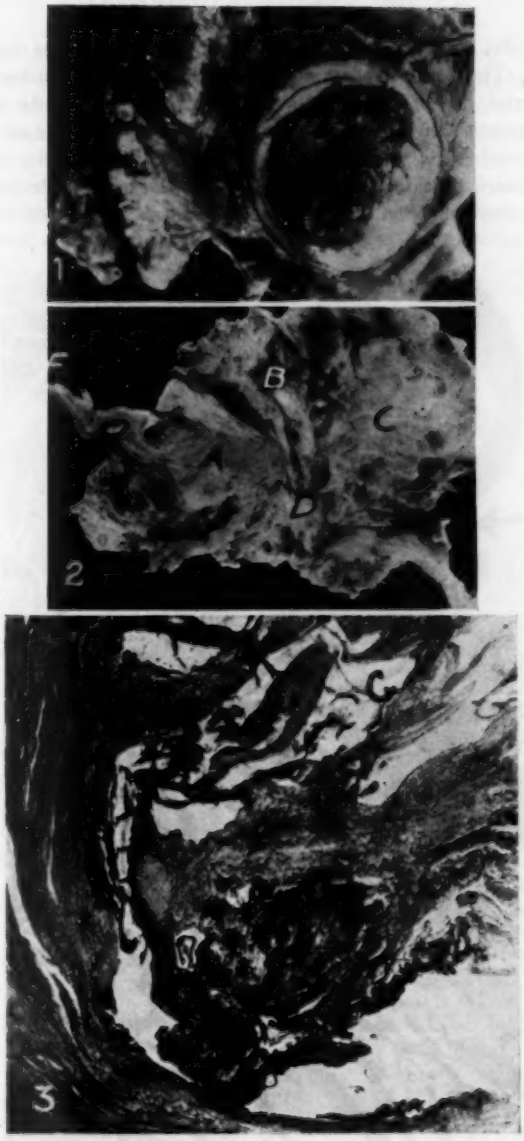

Fig. 1.—Photograph of the gross specimen showing the intravesical aspect of the neoplasm with the central nodular tumor surrounded by a seam of normal bladder mucosa.

Fig. 2.—This photograph represents a sagittal section made through the center of the tumor. *A* demonstrates the thickened, hypertrophied musculature of the bladder; *C*, the multiloculated, colloid-filled, cystic degenerated muscle tissue; *B-D*, the portion of the exposed urachal canal containing a calcified plug; *F*, a reflection of the supravesical cyst wall.

Fig. 3.—Photomicrograph of a cross section of the urachus, taken midway between *B* and *D* in figure 2. This shows the well developed wall on one side and a portion of the lumen, in which a dense fibrous plug, showing considerable calcification, is present. Extending laterally are the thin, irregularly shaped septums enclosing colloid-filled spaces. Rudimentary, flat epithelium can be observed in several places. (× 26.)

which many goblet cells may be seen. Most of the cells possess large oval nuclei, basally located. The greatest portion of the cell is usually transformed into dense mucinous material, which is poured into the crypt. Frequently the transitional epithelium reappears between the crypt openings on the surface of the tumor and disappears in another invagination. The deeper portions of the mass consist of large, multiloculated, cystic structures, frequently lined by a single layer of columnar cells as well as short cuboidal cells; all the cysts display advanced colloid degenera-

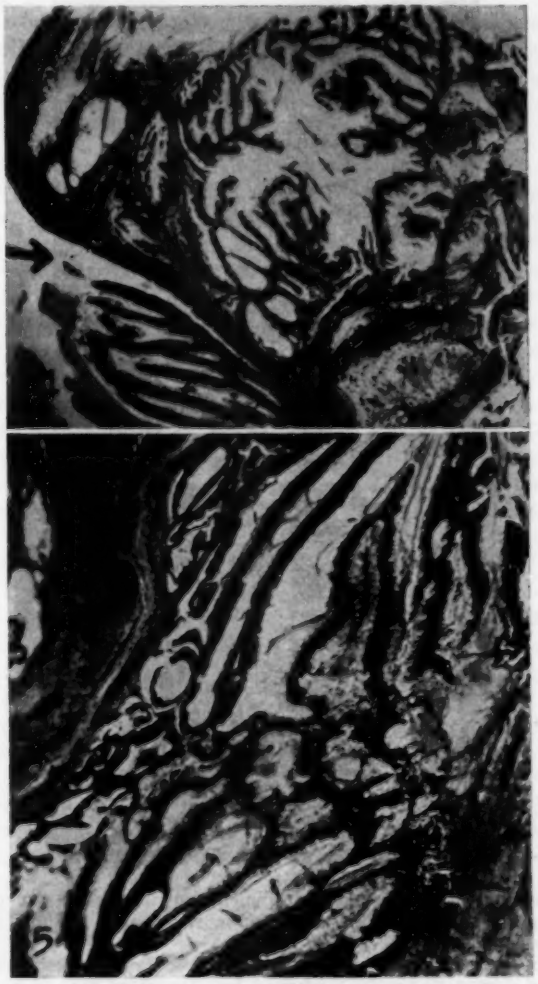

Fig. 4.—Photomicrograph of the surface of the intramucosal portion of the tumor disclosing the papillary, filigree-like arrangement of the epithelium, forming colloid-filled acini. The arrow indicates a crypt opening lined by transitional epithelium, below which are well formed mucous glands. (× 16.)

Fig. 5.—Photomicrograph showing highly differentiated glandular acini lined by tall columnar epithelium. The acini contain considerable mucinous material, and evidence of secondary infection may be observed. (× 112.)

tion, and the cavities are plugged with mucin. The septums are formed by thin, slender connective tissue bands which branch irregularly throughout the muscle and the submucosal coats. Many stages in the development of colloid carcinoma can be seen between well developed acini and pools of mucin possessing no cellular lining. The latter characteristic appears to predominate as one approaches the supravesical portion of the tumor, where the growth is far more irregular and disorderly. Longitudinal and cross (fig. 3) sections of the urachus disclose the presence of a definite lumen containing dense, calcified fibrous tissue showing some evidence of bone formation. At times the tubule possesses a rudimentary cuboidal epithelium, and at other times the epithelium is characteristically mucinous and columnar. There is marked hypertrophy of the smooth muscle layer, and a rather sharp line of demarcation is observed between it and the bulk of tumor on one side. On the other, however, the muscle layer is completely disintegrated by the irregular infiltration of branching glandular acini. There is severe granulocytic infiltration of the duct and its surrounding structures. Occasionally one finds accumulations of these cells leading to the formation of microscopic abscesses. The wall of the supravesical cyst is devoid of epithelium or of mucin-producing elements, although mucin is occasionally seen attached to its internal aspect.

COMMENT

The history of long-standing vague abdominal complaints, followed by hematuria and increasing signs of pathologic change in the lower genitourinary tract, associated with the cystoscopic appearance of the lesion, is quite characteristic of this tumor. The pathologic appearance of adenocarcinoma of the urachus and the lack of relationship of the tumor and the rectum or the colon are considered proof of the genesis of this neoplasm. It is interesting to note that the patient is the youngest on record. The case conforms otherwise, in all respects, to the criteria laid down by previous authors.

SUMMARY

Primary adenocarcinoma of the urachus involving the vault of the bladder occurred in a 26 year old man.

TERATOMA OF THE ANTERIOR MEDIASTINUM IN THE GROUP OF MILITARY AGE

A Study of Sixteen Cases, and a Review of Theories of Genesis

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Medical Corps, Army of the United States

THE study of teratoma in the light of modern embryology has been neglected by American pathologists. The purpose of this paper is to present an interpretation of the origin and the development of teratoma, with particular reference to that of the anterior mediastinum. The material for the study is provided by a series of 16 specimens of teratoma from 15 men and 1 woman within the military age group of 18 to 38 years.

The outstanding achivements of the experimental embryologists pertinent to our subject can be summarized briefly. In 1891 Driesch [1] observed that each of the first two or four blastomeres of a sea urchin's egg, if separated by shaking, can develop into a whole embryo. Three years later O. Schultze [2] found that when a fertilized frog ovum in the two cell stage was inverted a whole embryo developed from each of the two blastomeres. In 1929 Penners demonstrated that even after the four or the eight cell stage had been reached the experiment of Schultze would yield as many embryos as there were cells. The finding of such totipotency in amphibian blastomeres led to investigations on the fate of transplants exchanged between blastulas or early gastrulas. In this field the work of Spemann [3] and his students is prominent. It soon became apparent that before gastrulation the fate of each of the various regions of an embryo has not been determined. Thus, if a lateral piece of the blastula (presumptive skin) is excised and transplanted into the region of the presumptive neural plate of another blastula, it will form neural plate, not skin. Likewise, presumptive neural plate will form skin if transferred to the lateral region of the blastula. Similar results may even be obtained when tissue exchanges are made between regions that later develop into different germ layers. Thus, presumptive skin transplanted to the dorsal lip of the blastopore (presumptive mesoderm) is invaginated along with the surrounding cells to form mesodermal somites

From the Army Institute of Pathology, Washington 25, D. C.

1. Driesch, H.: Ztschr. f. wissensch. Zool. **53**:160, 1891.

2. Schultze, O.: Arch. f. Entwcklngsmechn. d. Organ **1**:269, 1894.

3. Spemann, H.: Embryonic Development and Induction, New Haven, Conn., Yale University Press, 1938.

and notochord. This exchange of cell groups between different presumptive germ layers has been widely interpreted as evidence for the nonspecificity of the germ layers.[4] However, a timely note of caution has been expressed by McCrady,[5] who emphasized the need for making a clear distinction between germ layers and presumptive germ layers; the latter are precusors of the former, but they are not identical with them. Hence, interchangeability of the presumptive germ layers does not signify that the germ layers themselves can be interchanged.

After completion of gastrulation the results of exchange transplantations are quite different. At these later stages the fate of each of the various regions has been determined, and the transplant follows its course of development uninfluenced by the new surroundings. A presumptive eye region if placed in the belly wall becomes an eye, not skin or muscle. The first region whose fate is determined is the presumptive mesoderm in the dorsal lip of the blastopore. If transplanted to an area of presumptive epidermis it does not form skin but sinks beneath the surface and there develops into somites or a notochord. After the implant has sunk beneath the surface a surprising phenomenon occurs; the overlying ectoderm, which normally would have produced skin, gives rise to a neural plate or even a secondary embryo. In other words, the implant has "induced" the formation of a neural plate. That is precisely what happens during normal development. Gastrulation consists in a large measure of a rolling in of presumptive surface mesoderm at the blastopore lip. The mesoderm then comes to lie immediately beneath the presumtive ectoderm, in which it "induces" the formation of a neural plate. The presumptive mesoderm has therefore been called the "primary organizer" of the amphibian embryo.

During the decade preceding the outbreak of the second world war, considerable progress was made in investigating the nature of the intracellular substance which acts as the organizer. In 1931 Spemann showed that crushing the cells had no deleterious effect on their inductive activity. In the following year several investigators working independently found that boiling the cells likewise did not affect their ability to induce organization. In fact, Holtfreter [6] demonstrated that after boiling, parts of the gastrula which formerly possessed no ability for induction now had acquired it. In 1933 the same investigator announced the discovery that adult tissues of all phyla will induce the formation of secondary embryos if implanted into amphibian blastulas.[7] Cell-free filtrates and numerous synthetic organic compounds have likewise induced the formation of

4. (*a*) Oppenheimer, J. M.: Quart. Rev. Biol. **15**:1, 1940. (*b*) Needham, J.: Biochemistry and Morphogenesis, London, Cambridge University Press, 1942.

5. McCrady, C., Jr.: J. Tennessee Acad. Sc. **19**:240, 1944.

6. Holtfreter, J.: Arch. f. Entwcklngsmechn. d. Organ **132**:225, 1934.

7. Holtfreter, J.: Naturwissenschaften **21**:766, 1933.

complex structures. Needham [4b] concluded that the natural organizer is a steroid, since besides the evidence of its chemical and physical characteristics "the only substance which so far has been shown to act in concentrations of the vitamin or hormone order is a polycyclic hydrocarbon."

The term "primary organizer" implies the existence of secondary and tertiary organizers. In several instances these had been identified before the concept of the primary organizer developed. The action of successive and increasingly specific organizers has been most completely elucidated for the eye. The primary organizer induces the formation of a neural plate which in turn becomes the central nervous system. Optic vesicles develop as lateral evaginations of the forebrain; subsequently they invaginate and are known as optic cups. The latter act as secondary organizers in that they induce the formation of a lens in the overlying ectoderm. If the optic cup is removed, no lens is formed; if displaced so that it lies beneath a portion of the ectoderm which normally becomes skin, the ectoderm will form a lens. A tertiary organizer is present in the lens and is responsible for the induction of changes in the overyling ectoderm leading to the formation of the transparent cornea.

In this brief summary the fascinating byways and perplexing problems of the subject cannot be considered. An excellent review of the chemical and physical methods of investigating embryogenesis, as well as a critical historical survey of developmental morphologic research, has been written by Needham.[4b] The implications of these studies for the understanding of teratoma will be considered in a subsequent section.

MATERIAL

The material on which this report is based comprises the clinical records and specimens of 16 cases of teratoma of the anterior mediastinum reviewed during the past four years at the Army Institute of Pathology.[8] Fourteen of the patients were soldiers, 1 was the wife of a soldier and 1 was a male civilian. Since all but the last were encountered in army hospitals, the preponderance of the male sex is of no significance. In view of the several million men under arms, every one of whom has had at least one routine roentgenologic examination of the chest, the incidence of mediastinal teratoma is low. Rusby [9] was able to find reports of 245 cases of teratoma in the literature at the end of 1939 and added a report of 6 of his own. In the present study the cases are arranged in two groups: In the first group, 10 cases, the tumor was benign; in the remaining 6 it was cancerous.

GROUP I. BENIGN TERATOMA

Of the 10 patients of this group, the oldest was 36 years of age, the youngest 20; the average age was 24 years. Two patients (cases 3 and 8) were wholly without signs or symptoms, the growths being discovered

8. An additional case has been previously reported by S. J. Wilson and R. Cares (Arch. Path. **39**:113, 1945).

9. Rusby, N. L.: J. Thoracic Surg. **13**:169, 1944.

in routine roentgenograms of their chests. The other patients had symptoms for periods ranging from two weeks to two years; the average duration was approximately four months. In 5 patients the presenting symptom was pain in the chest, followed by cough and dyspnea; 3 patients complained of shortness of breath and cough before they experienced any pain. Seven patients recovered completely after operative removal of their tumors. Two died soon after operation; a third died from compression of mediastinal structures.

REPORT OF CASES

CASE 1.—*Clinical Course.*—A 23 year old white soldier complained of a deep pressing ache in the right side of his chest about September 1942. Roentgenograms of the chest taken at that time were interpreted as showing cardiac enlargement, a diagnosis that was repeated when similar studies were made the following year. The thoracic pain recurred at intervals, was located to the right of the sternum between the third and the fourth rib and did not radiate. In August 1944 an acute

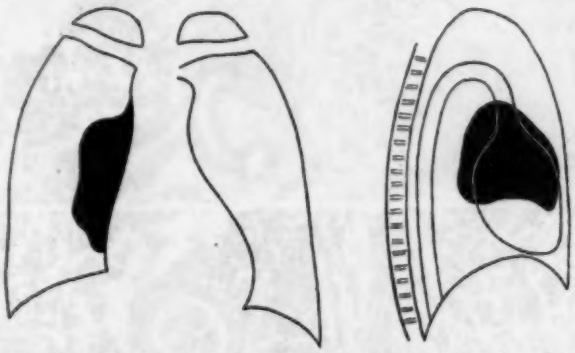

Fig. 1 (case 1).—Diagram of the roentgen shadows in the right lung field. The outline drawings which illustrate the cases are copied from representative roentgenograms of the chests of the patients. The part of the tumor that encroached on the lung field is shown in solid black, the portion in the precardial region cannot be distinguished from the shadow of the heart and large vessels. If the tumor outline is indefinite, this will be indicated by cross hatchings; fluid in the pleural cavity is represented by horizontal lines. In a few figures, both frontal and lateral views are given.

febrile illness developed, and at that time roentgenograms of the chest revealed a circumscribed dense homogeneous shadow, 5 by 7.5 by 10 cm., at the anterior medial border of the right lung field (fig. 1.). Cutaneous tests with coccidioidin, tuberculin and hydatid cyst fluid were negative. At operation, two months later, a large cystic tumor was found in the anterior mediastinum, attached to the pericardium and displacing the hilus of the right lung. The firm pericardial attachment of the tumor made sharp dissection impossible, necessitating piecemeal removal. Postoperative recovery was uneventful.

Gross Examination.—The specimen consisted of several large pieces of cyst wall, 2 to 5 mm. in thickness. The lining surface was granular and red, owing to scattered deposits of old blood pigment.

Microscopic Examination.—The cyst wall consisted of dense, partly hyalinized connective tissue. Attached to the outer surface were small masses of thymus (fig. 2*C*). The following components were recognized:

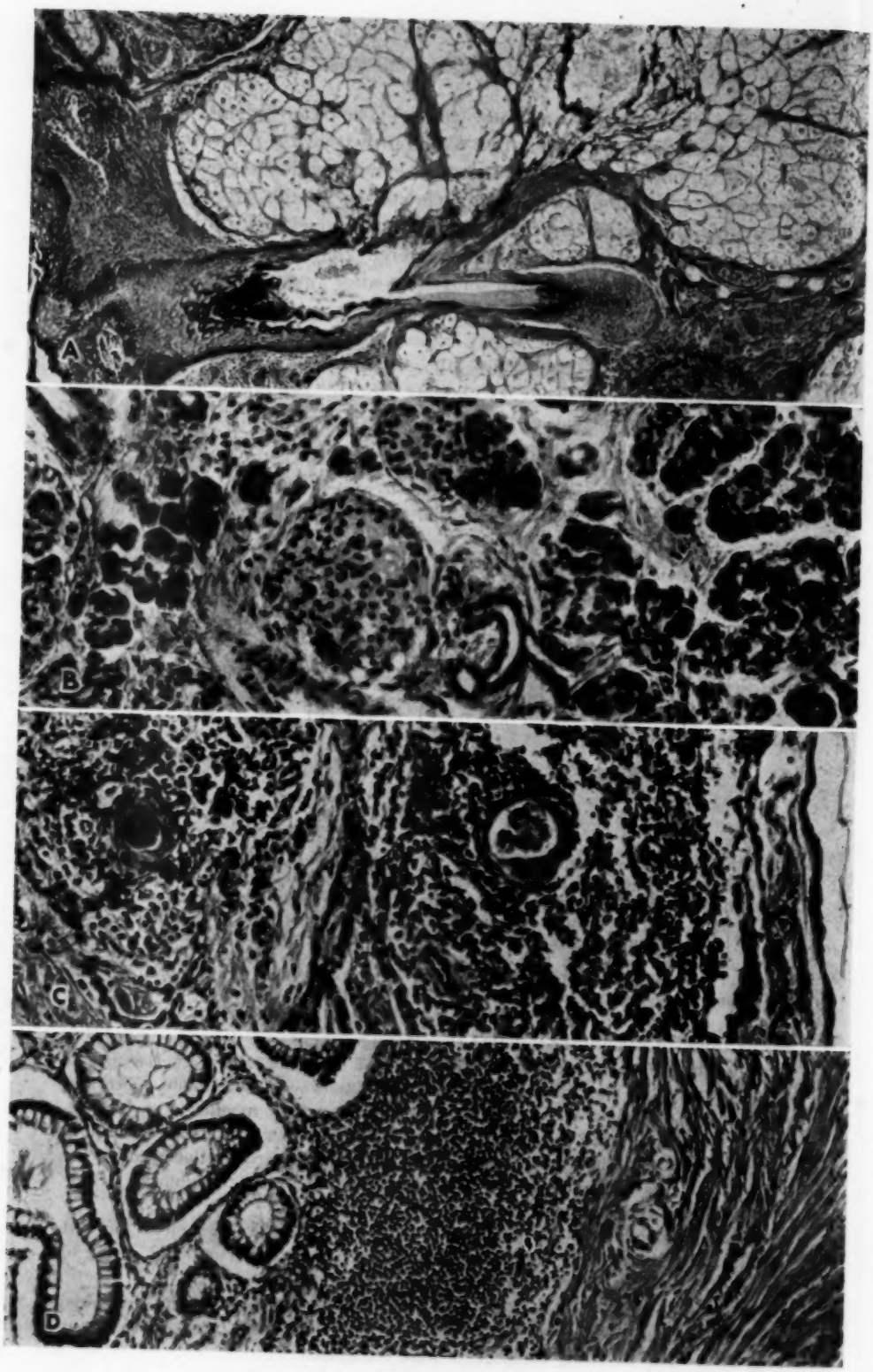

Figure 2

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(*a*) Ectodermal Derivatives: Most of the lining epithelium of the cyst had disappeared; however, in some areas stratified squamous epithelium remained. Associated with this were hair follicles, sebaceous glands (fig. 2*A*) and sweat glands.

(*b*) Mesodermal Derivatives: Several isolated masses of smooth muscle were present. Scattered islands of fat cells separated the bundles of connective tissue. The blood vessel walls were well developed. Hyaline cartilage was found associated with ciliated epithelium.

(*c*) Entodermal Derivatives: Ciliated columnar epithelium formed the lining of structures resembling bronchi. These contained islands of cartilage and mucous glands; the acini of the latter often contained demilunes of serous cells. Pancreas with well developed acinous tissue, dilated ducts and islets of Langerhans were abundant (fig. 2*B*).

Case 2.—*Clinical Course.*—A 23 year old white soldier was admitted to the hospital for treatment of a shrapnel wound of the right leg. During convalescence he complained of pain in the chest. A roentgenogram revealed a large mass in the upper part of the anterior mediastinum with some evidence of tracheal compression. Surgical removal of the tumor was undertaken; although it was adherent to the pleura and the aortic arch, the mass was freed and removed intact. While the wound was being closed there was sudden profuse bleeding from the aorta. Attempts to control the hemorrhage failed, and the patient died.

Gross Examination.—The tumor measured 8 by 5 by 5 cm., had a smooth, somewhat lobulated surface, and on section was found to contain many cystic spaces filled with a clear viscid fluid. The cysts were separated by firm fibrous tissue containing several areas that were cartilaginous in consistency.

Microscopic Examination.—Only three blocks of tissue were available for histologic examination; the rest of the material was lost in transit as a result of enemy action.

(*a*) Ectodermal Derivatives: No tissue of this germ layer could be recognized with certainty. Small patches of squamous cell epithelium were probably metaplastic derivatives of the columnar ciliated epithelium with which they were associated.

Explanation of Figure 2

A, section of the lining epithelium of the large cyst (case 1), showing differentiation into skin and its appendages. At the lower left is a portion of stratified squamous epithelium of the surface which extends inward about the shaft of a hair. The hair is cut tangentially; only the basal portion of the shaft and the well developed hair follicle are shown in the section. A large sebaceous gland opens into the connective tissue sheath of the hair. Masson's trichrome stain; × 100.

B, pancreatic tissue (case 1) containing both islets of Langerhans and acinous cells. At the center are two islets. Just below and to the right of center is a prominent duct. Darkly staining acini and supporting stroma occupy the remainder of the figure. × 500.

In *C*, on the extreme right, is shown the surface of the cystic teratoma (case 1). Incorporated in the wall is thymic tissue, recognizable in the figure as collections of lymphocytes containing two Hassall's corpuscles. × 230.

D, structure resembling large intestine (case 3). The "mucosa" is made up of tubular glands lined by goblet cells. A distinct "muscularis mucosae" is not present. In the narrow "submucosa" is a collection of lymphoid tissue, beneath which lie circular bundles of smooth muscle. × 145.

(*b*) Mesodermal Derivatives: The connective tissue was loosely reticulated and contained many dilated vascular spaces with poorly developed walls. Differentiating between lymphatics and blood vessels was often difficult. Stout bundles of smooth muscle coursed in various directions, unassociated with other structures.

(*c*) Entodermal Derivatives: The cysts noted grossly were lined by cuboidal and columnar ciliated epithelium. They were unaccompanied by the smooth muscle or the cartilage so frequently observed in these tumors. Occasional small masses of lymphoid tissue lay adjacent to the epithelium. Several small cysts were lined by cuboidal cells devoid of cilia and distended with mucus. In one area was a structure resembling an islet of Langerhans, associated with small ducts and acini. The cells of the latter stained deeply with eosin in the manner of the acinous cells of the pancreas.

Case 3.—*Clinical Course.*—A 20 year old white soldier had no symptoms referable to the chest, and routine roentgenologic examination of the chest disclosed a mediastinal mass (fig. 3). Three months later operation was performed for removal of the tumor.

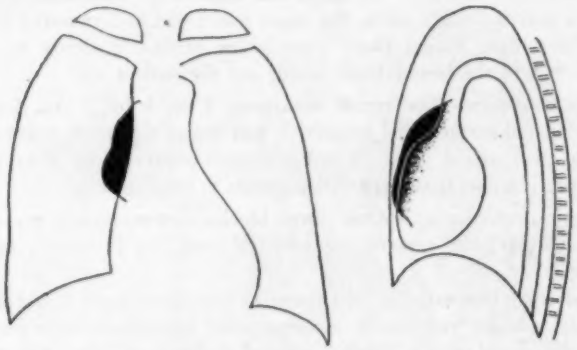

Fig. 3 (case 3).—Diagram of the roentgen shadows of the mediastinal mass.

Gross Examination.—The tumor was spherical and fluctuant, weighed 592 Gm. and measured 13.5 by 9 by 8.5 cm. The free surface was smooth and glistening; the area of attachment to the mediastinal structures was roughened. When bisected, the mass was seen to consist of several confluent cystic spaces (fig. 4) containing a total of 490 cc. of dark brown watery fluid. Arising from the inner surface of a 5 by 4 cm. cyst was a pedunculated small white papilloma having a granular, hair-bearing surface suggestive of skin.

Microscopic Examination.—Attached to the outer surface of the teratoma were flattened remnants of the thymus gland. Hassall's corpuscles could be readily identified.

(*a*) Ectodermal Derivatives: The papilla described grossly was covered by well differentiated skin, bearing hair follicles as well as sweat and sebaceous glands.

(*b*) Mesodermal Derivatives: Smooth muscle and adipose tissue were present beneath the skin covering the papilla. The muscle bundles were also found surrounding organoid alimentary and respiratory structures. Associated with the latter were islands of hyaline cartilage; lymphoid tissue was present beneath both the intestinal and the bronchial type of epithelium.

(*c*) Entodermal Derivatives: Prominent in many sections were goblet cell or mucous epithelium and ciliated columnar epithelium. Both were frequently associated with the mesodermal structures already noted, so that they closely resembled cross sections of large intestine (fig. 2*D*) or bronchi. Mucous and serous glands

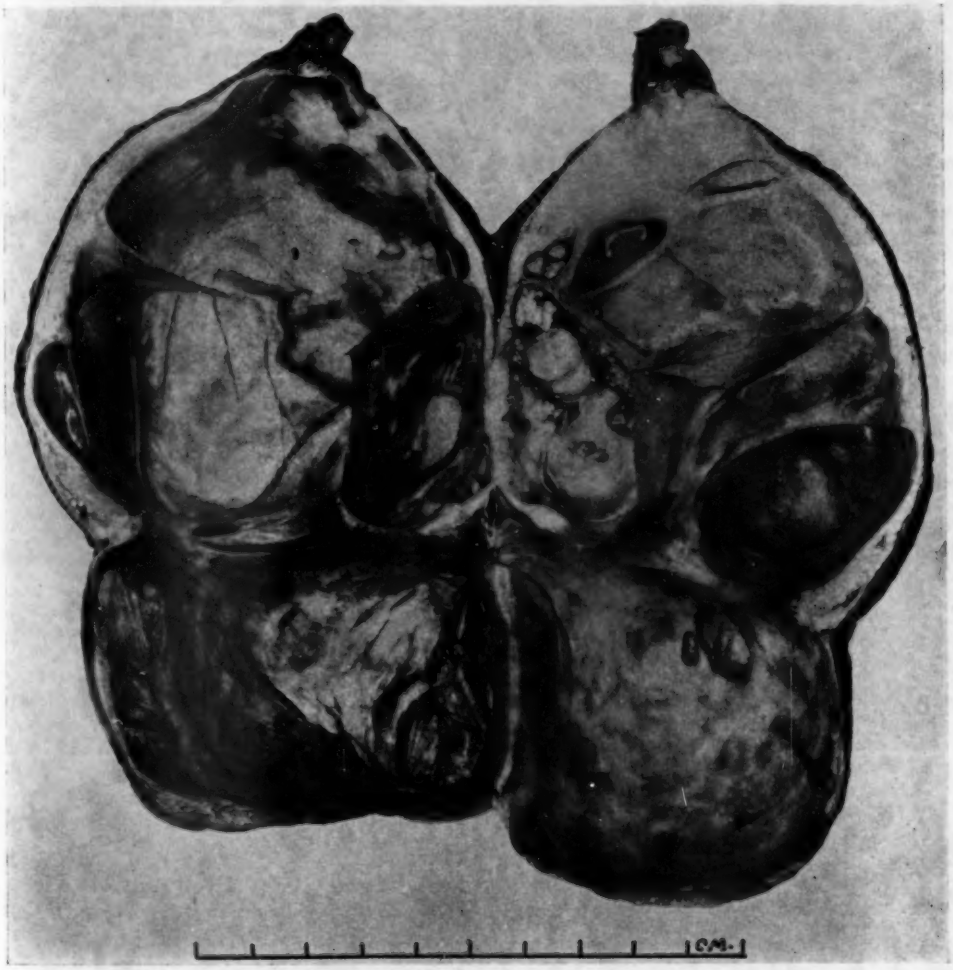

Fig. 4 (case 3).—The teratoma has been opened by a median vertical section. Before it was opened the specimen weighed 592 Gm. and was filled with 490 cc. of dark brown fluid. It measured 13.5 by 9 by 8.5 cm. Thin septums extend inward from the wall converting the large cavity into a multilocular cyst. Arising from the inner surface of one of the cysts is a papilloma (just above and to the right of the center of the teratoma) covered by granular, hair-bearing skin.

were often found in the walls of the latter. Large masses of typical pancreatic acinous tissue in close relation to ducts and islets of Langerhans were conspicuous in several sections (fig. 5*A*).

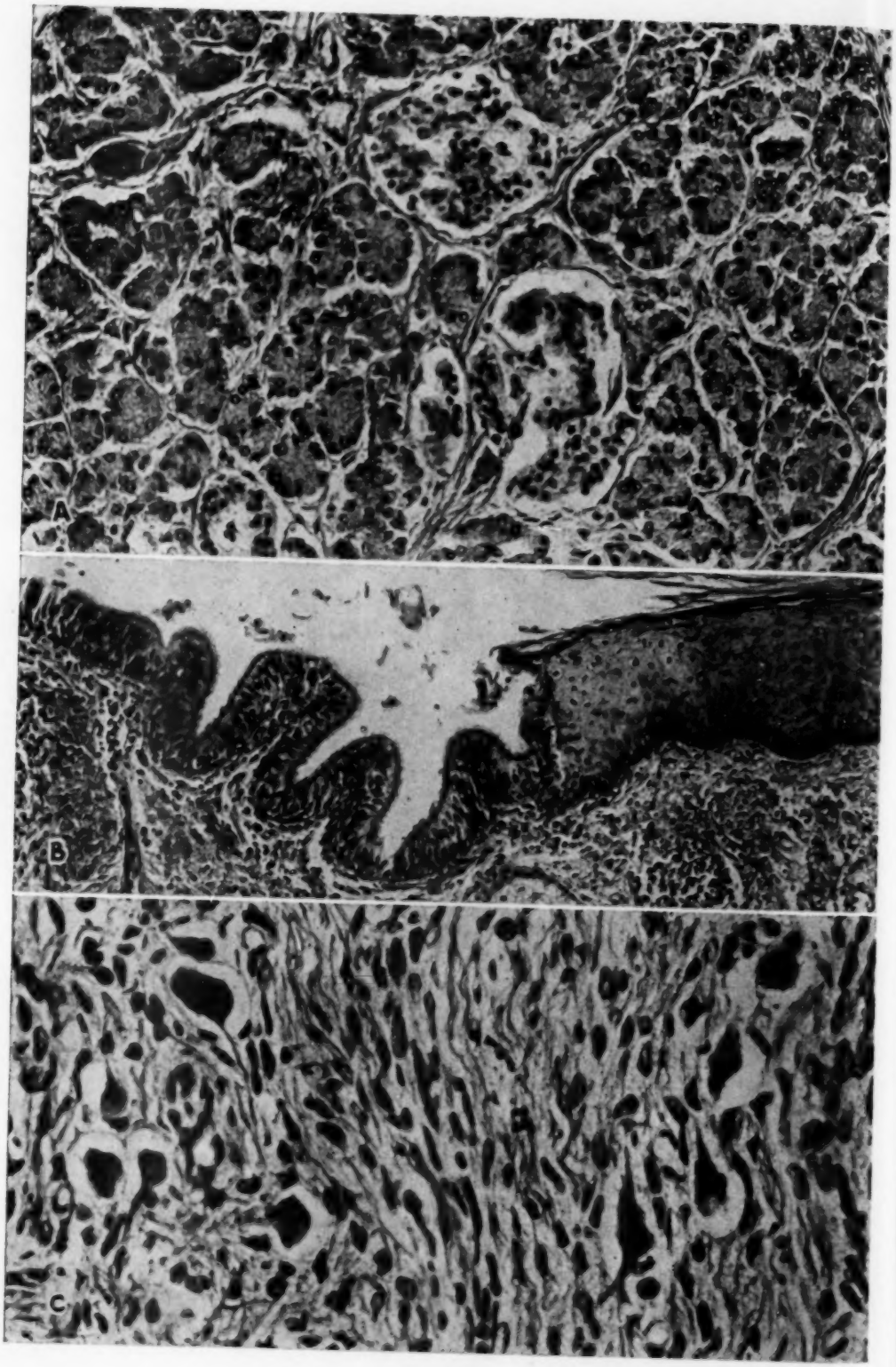

Figure 5

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CASE 4.—*Clinical Course.*—A 23 year old white soldier began to have symptoms of illness nine months before his death. These consisted of attacks of severe epigastric pain and vomiting, occasionally associated with a sensation of squeezing about his heart. He began to lose weight and felt chronically ill. A roentgenogram of the chest made a month after the onset of symptoms revealed a tumor in the anterior mediastinum (fig. 6). High voltage roentgen therapy with a total dosage of 1,000 roentgens (r) produced no change in the lesion. Thoracoscopy, carried out at the fifth left interspace, disclosed a smooth, round, yellowish tumor, apparently arising in the anterior mediastinum. An exploratory thoracotomy with approach through the left side of the chest confirmed these findings and likewise demonstrated firm union of the pericardium with the tumor. Removal of the mass was not attempted at that time. After the wound had healed, thoracotomy was performed by way of the right side of the chest. The tumor was tense and cystic; 700 cc. of thin milky fluid was aspirated before removal was attempted. The lower portion of the neoplasm was readily separated from the surrounding tissue, but in the region of the thymus the adhesions were so dense that not all of the tumor could be excised. During the operation the patient went into shock, from which he only partially recovered. After a few hours his temperature rose, convulsive movements of his left arm occurred, and he died.

Gross Examination.—The specimen consisted of an irregular, ragged cyst wall, from which fragments of tissue had been cut or torn during removal. It measured approximately 13 by 6 cm. and was 2 mm. in thickness. Near one pole the wall was thickened as a result of the presence of many firm nodules, some of which were covered by hair-bearing "skin."

Microscopic Examination.—(*a*) Ectodermal Derivatives: Many cysts were lined by squamous epithelium, often associated with hair shafts, sebaceous glands and sweat glands. In several regions the "skin" was abruptly replaced by ciliated columnar epithelium (fig. 5*B*).

(*b*) Mesodermal Derivatives: Bundles of smooth muscle were found in association with the "skin" or the ciliated epithelium, beneath which were occasional collections of lymphoid tissue containing well differentiated germinal centers. Adipose tissue appeared in irregular islands that had no definite relation to surrounding structures.

(*c*) Entodermal Derivatives: Ciliated columnar epithelium lined several small cysts. Occasionally, organoid respiratory structures were found to contain mucous glands. Prominent in several sections were large masses of pancreatic acinous tissue associated with dilated ducts and islets of Langerhans.

CASE 5.—*Clinical Course.*—About November 1942 a 29 year old white soldier first noticed throbbing pain in the precordial region after exercise. These attacks became more frequent and of longer duration, accentuated by an accident in which the patient wrenched his back. A roentgenogram of the chest taken at this time (September 1943) revealed an intrathoracic tumor. Roentgen therapy to a total

EXPLANATION OF FIGURE 5

A, well differentiated pancreas (case 3). At the center are two islets of Langerhans. × 230.

B, wall of a small cyst lined by pseudostratified ciliated columnar epithelium and stratified squamous epithelium (case 4). The transition between the two epithelia is abrupt. × 160.

C, neuroglia and ganglion cells, some of the latter with visible axis-cylinders and dendrites. (case 6). Bodian's silver-aniline blue stain; × 500.

dosage of 1,000 r was given without apparent effect on the size of the lesion. A diagnosis of teratoma of the anterior mediastinum was made. In March 1944, a year and four months after the onset of symptoms, a thoracotomy was performed and the tumor excised. In August 1944 the patient was transferred to a convalescent center with recommendation for return to duty.

Gross Examination.—The tumor, which measured 7.5 by 6.5 by 6 cm., was well encapsulated and fluctuant. The wall, 5 mm. thick, enclosed a space filled with sebaceous material and hair. The smooth lining surface bore several nodules from which arose long hairs.

Microscopic Examination.—(*a*) Ectodermal Derivatives: These were represented by skin with its appendages of hair, sebaceous glands, sweat and apocrine glands. (*b*) Mesodermal Derivatives: These were represented by adipose and connective tissue from the supporting stroma of the cyst wall. Beneath the epidermis were many parallel bundles of smooth muscle. Large lymphatic channels were prominent in several sections. Collections of lymphoid tissue were likewise present. Areas of necrosis in which no structural details were recognizable were attributable to preoperative irradiation.

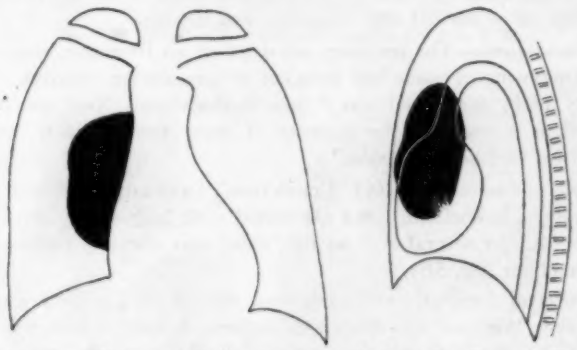

Fig. 6 (case 4).—Diagram of the roentgen shadows in the anterior mediastinal field.

(*c*) Entodermal Derivatives: Several cysts were lined by columnar ciliated epithelium, beneath which bundles of smooth muscle were frequently found. However, more complex organoid respiratory structures containing cartilage and mucous glands were absent.

CASE 6.—*Clinical Course.*—A 22 year old white soldier was well until August 1941, when fleeting pains began to occur in the upper anterior part of the left side of the chest and the left arm. Four months after the onset of these symptoms, which had become progressively more severe, the patient became dyspneic and began to have a moderate, nonproductive cough. A roentgenogram of the chest revealed a well circumscribed tumor arising in the anterior mediastinum and encroaching on the hilus of the left lung (fig. 7). At operation (February 1942) a cystic mass was found densely adherent to the pericardium; it extended laterally as far as the nipple line and displaced the left lung posteriorly. To the right it passed beyond the median line of the sternum and extended down to the fifth intercostal space. The superior border of the lesion passed along the arch of the aorta. Recovery was uneventful.

Gross Examination.—The tumor was spherical and cystic and measured 10 by 10 by 12 cm. The surface attached to the pericardium was roughened; elsewhere

it was smooth and glistening. It varied in color from yellowish pink to white. The smooth surface was interrupted by six scattered nodules varying in diameter from 1 to 4 cm., with a maximum elevation of 1.5 cm. On the side opposite the pericardial attachment there was a cordlike structure 9 cm. in length and 0.5 cm. on cross section. Histologic examination showed this to be normal thymus gland. The cut surfaces of the tumor were composed of lobules of fatty tissue separated by strands of white fibrous tissue that blended into cartilage. Cysts, ranging from 1 to 15 mm. in diameter, with rather thick walls, were scattered through the mass. Some of the larger cysts contained sebaceous material, which in one was mixed with hair.

Microscopic Examination.—(*a*) Ectodermal Derivatives: Many of the cysts were lined by skin bearing well differentiated hair follicles, sebaceous glands and sweat glands. In one region there were numbers of ganglion cells with well developed axons and dendrites surrounded by neuroglia (fig. 5*C*).

(*b*) Mesodermal Derivatives: Hyaline cartilage, usually in close association with ciliated columnar epithelium, was abundant. In some regions the cartilage cells had taken axial positions and were associated with endochondral bone formation (fig. 8*A*). Between the interstices of this bone there was active hemopoietic

Fig. 7 (case 6).—Diagram of the roentgen shadows in the anterior mediastinal field.

tissue. Membranous bone formation was also present in several areas (fig. 8 *B* and *C*). Lymphoid tissue with occasional follicle formation was frequently seen adjacent to "intestinal" and "bronchial" epithelia. The latter were often surrounded by smooth muscle; in other regions smooth muscle had formed large masses unassociated with epithelial structures (fig. 8*D*). Adipose tissue was scattered throughout the sections.

(*c*) Entodermal Derivatives: Many spaces were lined by ciliated columnar epithelium, which in turn was surrounded by hyaline cartilage, smooth muscle and mucous and serous glands—a fair reproduction of a bronchial wall. Similarly, mucous epithelium, associated with smooth muscle and lymphoid tissue, duplicated a section of the large intestine (fig. 9*A*). Masses of dark-staining epithelial cells, containing large acidophilic zymogen granules, are arranged in acini. These cells, representing pancreas, are found in association with typical ducts and islets of Langerhans.

CASE 7.—*Clinical Course.*—A 36 year old white soldier complained of slight dyspnea, which had been present for many years. A roentgenogram of the chest revealed a mass in the upper part of the anterior mediastinum, to the left of the

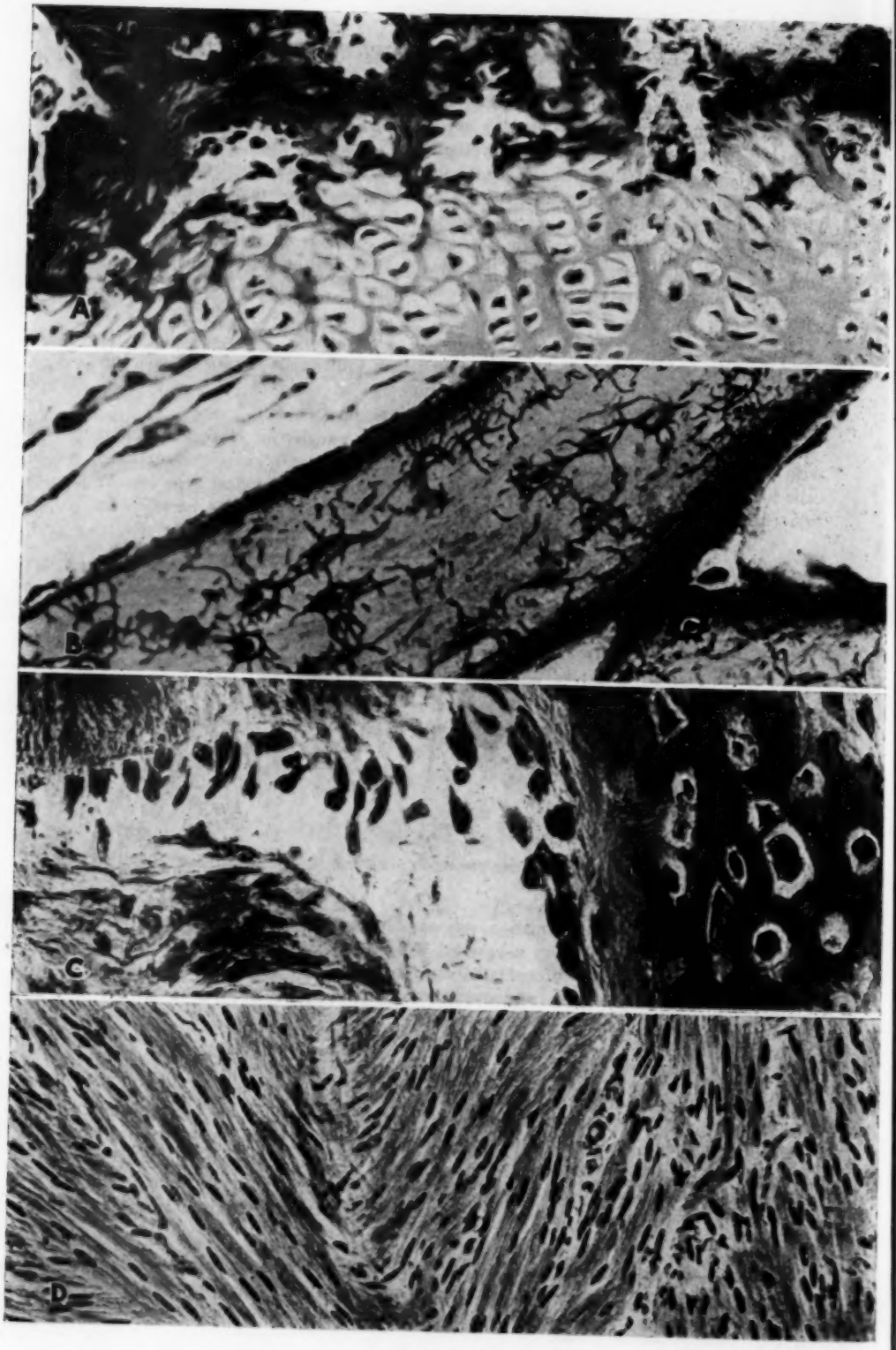

Figure 8

(See legend on opposite page)

heart, near the pulmonary artery (fig. 10). Within two months pain developed in the left shoulder, and the patient had severe dyspnea, cough and fever. These symptoms subsided only to recur after another lapse of three months. At this time another roentgenogram of the chest showed considerable increase in the size of the mediastinal mass. The tumor was removed surgically.

Gross Examination.—The specimen was a cyst measuring 5.5 by 6 by 5 cm. The external surface was smooth and glistening except for several irregular hemorrhagic granular areas where the tumor was adherent to the pleura. The cyst was filled with hair and sebaceous material. The lining was smooth except for several polypoid masses, the largest of which measured 2 by 2.5 cm. The cyst was covered by "skin" having the texture of orange peel and bearing many fine lanugo hairs (fig. 9*B*). On section this polypoid structure was seen to consist almost solely of adipose tissue.

Microscopic Examination.—(*a*) Ectodermal Derivatives: The surface of the polypoid mass was covered by well differentiated skin (fig. 9*D*). The sebaceous and sweat glands were well developed, as were also the hair follicles. Large bundles of smooth muscle ran obliquely and parallel to the surface; often they were attached to the connective tissue sheath of the hair follicles as arrectores pilorum.

(*b*) Mesodermal Derivatives: Prominent in this group was the adipose tissue which made up the bulk of the polypoid masses noted grossly. The smooth muscle of the skin contributed to the well differentiated appearance of the structure. Smooth muscle was also found about spaces lined by ciliated columnar and mucous epithelium. In the latter connection it was arranged in both longitudinal and circular layers. A large mass of smooth muscle contained several cystic spaces lined by cuboidal epithelium. This structure resembled the normal prostate. Lymphoid tissue was often associated with both the mucous and the ciliated columnar epithelium; islands of hyaline cartilage, with the latter.

(*c*) Entodermal Derivatives: Irregular, often elongated and elaborately branching spaces were lined by ciliated columnar epithelium and occasional goblet cells. Accompanying these were mixed mucous and serous glands associated with hyaline cartilage, smooth muscle and lymphoid tissue. The whole organoid structure was a fair replica of a bronchiolar wall (fig. 9*C*). However, it was unlike a normal bronchus in that the ciliated epithelium was often abruptly replaced by stratified squamous cells. An epithelium consisting of goblet cells and accompanied by circular and longitudinal bundles of smooth muscle and lymphoid tissue closely resembled the wall of the appendix or the large intestine. Most prominent in these sections, however, were masses of well differentiated pancreas consisting of acini, islets of Langerhans and ducts.

EXPLANATION OF FIGURE 8

(Case 6). *A*, endochondral bone formation. Lamellar bone has been laid down about advancing capillaries, which are invading degenerating cartilage cells; the latter have taken up an axial position. × 230.

B, bone lamellas showing osteocytes within the lacunas. Canaliculi radiate from the lacunas. Bodian's silver-aniline blue stain; × 500.

C, membranous bone formation. The lamellas of bone are lined by osteoblasts, some of which have been incarcerated within the developing bone as osteocytes. × 280.

D, interlacing bundles of smooth muscle resembling a leiomyoma in appearance. Bodian's silver-aniline blue stain; × 230.

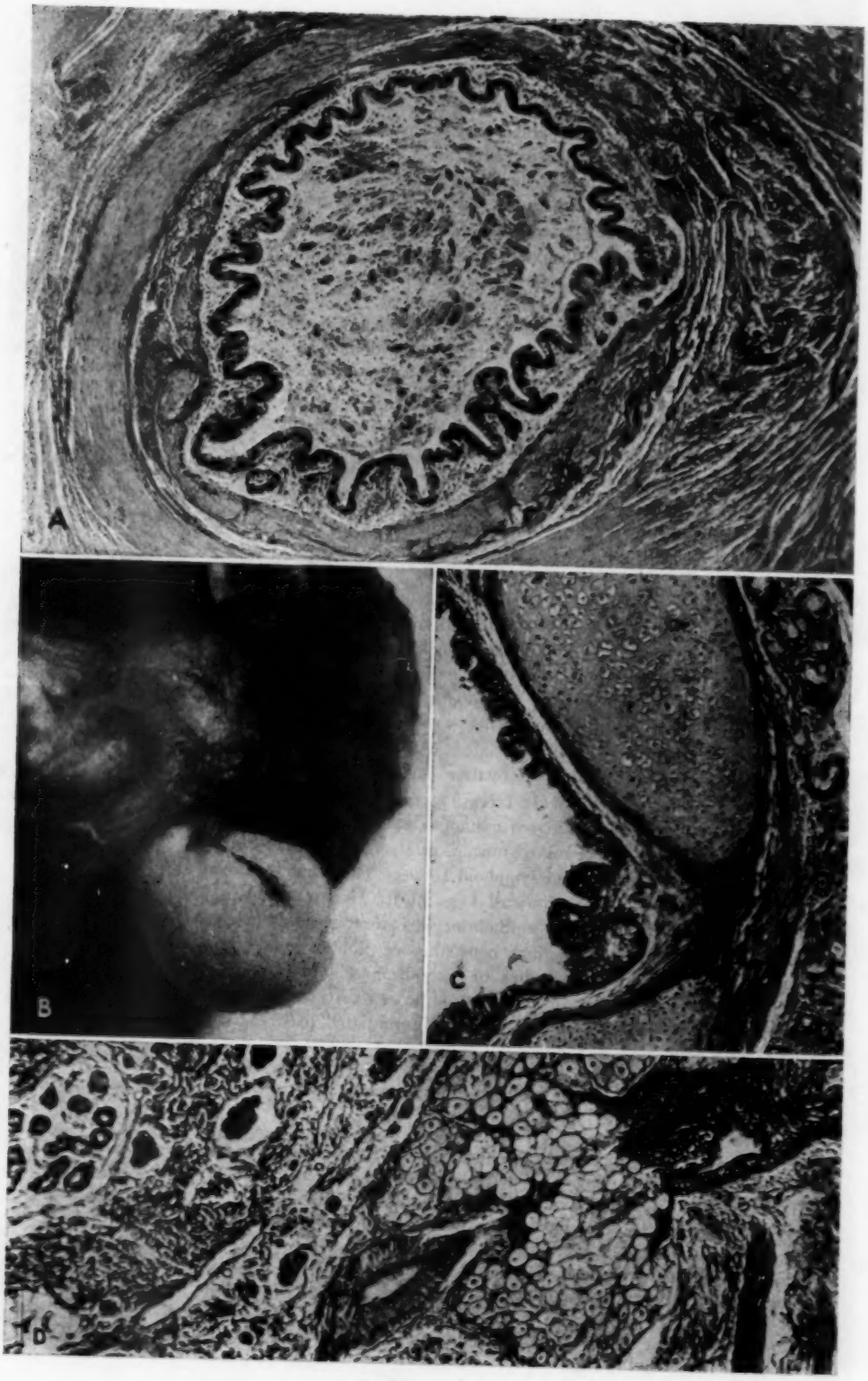

Figure 9

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CASE 8.—*Clinical Course.*—A roentgenogram of the chest, made as part of a routine physical examination of a 20 year old white soldier, revealed in the anterior mediastinum a mass showing atypical calcification (fig. 11). There was no history of any symptoms referable to the lesion of the chest. Physical examination gave wholly negative results. At operation a cystic tumor was found "deep" in the mediastinum and removed intact. A hemopneumothorax developed but was resorbed; otherwise recovery was uneventful.

Gross Examination.—The specimen was a thick-walled cyst, measuring 9 by 5 by 5 cm. On section the lining surface was smooth, and the lumen was filled with sebaceous material and hair which arose from several small, partly calcified nodules.

Microscopic Examination.—(*a*) Ectodermal Derivatives: The surface of the nodules noted grossly consisted of stratified squamous epithelium, beneath which lay numerous sebaceous glands that were frequently associated with hair follicles. The sebaceous glands were very large, approaching adenomatous proportions. Several dilated sweat glands or apocrine glands were also present.

(*b*) Mesodermal Derivatives: Bundles of smooth muscle and groups of fat cells were scattered throughout the dense, hyalinized connective tissue which formed the supporting stroma of the cyst wall. In several regions there were irregular spaces, probably lymph channels, that closely resembled those seen in lymphangioma. Many of the spaces contained numbers of large macrophages having foamy cytoplasm. Collections of lymphoid tissue were frequently seen close by.

(*c*) Entodermal Derivatives: Organoid alimentary structures lined by tall columnar mucous epithelium and surrounded by well differentiated layers of smooth muscle were prominent.

CASE 9.—*Clinical Course.*—A 23 year old white woman, wife of a soldier, had had a "leaking heart" since the age of 6 years. She had been a sickly child, unable to take exercise because of shortness of breath. Recurring hemoptysis became more frequent and severe. On admission to the hospital the patient was underweight and pale, with pronounced clubbing of fingers and toes. The pulse was rapid and the heart enlarged, and a diastolic murmur was heard at the apex. The cardiac signs disappeared on rest and symptomatic treatment. Roentgenograms of the chest showed a mass in the middle lobe of the right lung, in which teeth and calcium deposits were clearly visible.

EXPLANATION OF FIGURE 9

A, organoid structure resembling a portion of the large intestine (case 6). The mucosa is lined by goblet cells. A muscularis mucosae and lymphoid tissue, however, are absent. × 70.

B, cystic teratoma (case 7) which has been opened and its contents of hair and sebaceous material removed. A sessile polyp, 2 by 2.5 cm., projects into the cavity. The surface of the polyp has the texture of orange peel and bears many delicate hairs.

C, portion of the wall of an organoid respiratory structure or "bronchus" (case 7). The lumen is lined by ciliated columnar epithelium. This is separated from the adjacent hyaline cartilage by a narrow band of connective tissue. Below the cartilage are numerous mucous glands. × 100.

D, well differentiated skin from the polyp shown in *B* (case 7). A hair follicle, a hair sheath and an accompanying sebaceous gland are clearly shown, cut slightly off center. At the right are the oblique smooth muscle bundles of the arrectores pilorum. At the left margin is a coiled sweat gland. × 120.

At operation the middle lobe was found to be atelectatic and adherent to the thoracic wall. It had been displaced by a large cystic tumor which apparently arose in the anterior mediastinum and was intimately united with the pericardium. The neoplasm and the right middle lobe were removed; recovery was uneventful.

Gross Examination.—The tumor was a well encapsulated cystic mass weighing 450 Gm. and measuring 15 cm. in diameter (fig. 12*A*). The cyst wall averaged 2 mm. in thickness; on its inner surface it bore several papillary projections from which arose many long hairs. The largest of the papillae was broadly sessile,

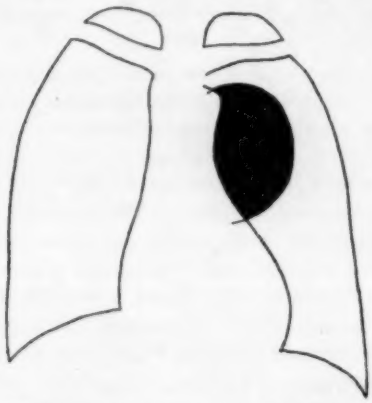

Fig. 10 (case 7).—Diagram of the roentgen shadow in the upper part of the anterior mediastinum.

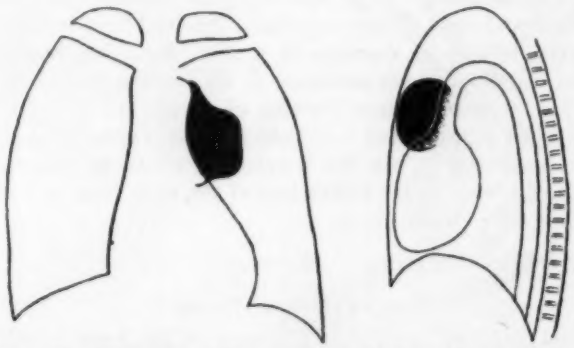

Fig. 11 (case 8).—Diagram of the roentgen shadow of a mass in the anterior mediastinum.

almost spherical in shape, and 4 cm. in diameter. On section it consisted primarily of adipose tissue. The skin that covered the papillae had a coarse "orange peel" texture. Attached to a portion of the cyst wall was an irregular piece of bone (4 by 5 by 2 cm.) bearing three visible teeth. The cyst cavity was filled with densely packed hair matted together with sebaceous material.

Microscopic Examination.—(*a*) Ectodermal Derivatives: The cyst wall, which contained remnants of the thymus gland, was composed of dense bundles of connective tissue and was lined by stratified squamous epithelium. The epithelium and underlying connective tissue had the appearance of true skin, containing well

differentiated sebaceous glands, usually associated with a hair follicle. Dilated sweat glands, often resembling apocrine glands, were likewise found. The teeth noted grossly had a histologic structure identical with that of normal teeth (fig. 12 *C*). The columnar odontoblasts were clearly visible at the base (fig. 12 *B*). The characteristic lamellar structure of the bone surrounding normal teeth was also present. Abnormal, however, was the finding of mixed mucous and serous salivary glands and ciliated columnar epithelium in intimate relation with the alveolar bone.

(*b*) Mesodermal Derivatives: Narrow bundles of smooth muscle, oblique to the surface of the epidermis, were frequently attached to the connective tissue sheath of the hair follicles, closely resembling normal arrectores pilorum. Smooth muscle, arranged in circular parallel bundles, was also seen, surrounding spaces lined by mucous or ciliated columnar epithelium. Elsewhere were irregular masses of smooth muscle with no apparent relation to other structures. Bone was present only in association with teeth. In some areas haversian canals with concentrically arranged lacunas were prominent. Between the bone trabeculae lay hemopoietic tissue identical with that found in normal active marrow. Hyaline cartilage was widely scattered throughout all sections, usually closely associated with ciliated columnar ("bronchial") epithelium. Occasionally, however, no such relation could be demonstrated. Lymphoid tissue, frequently containing well differentiated germinal centers, was often observed lying immediately beneath the columnar epithelium. Patches of adipose tissue were numerous and usually were surrounded by bundles of collagenous connective tissue. Blood vessels with well developed walls were abundant.

(*c*) Entodermal Derivatives: Prominent in all sections were small cystic spaces lined by squamous, mucous or ciliated columnar epithelium. Many of the cysts were lined wholly or predominantly by one of these three types of epithelium. In such instances, particularly in the presence of smooth muscle and lymphoid tissue, the resultant organoid structures resembled bronchi and intestine. Other cysts bore all three varieties in almost equal proportions. The squamous epithelium, however, was probably a metaplastic derivative of the columnar type. In one area, associated with mucous ("intestinal") epithelium, were numerous acini, the cells of which contained large eosinophilic zymogen granules. Nearby were spaces lined by tall columnar epithelium similar to that normally observed lining large excretory ducts. Despite the absence of islets of Langerhans, this tissue was histologically identical with pancreas.

Case 10.—*Clinical Course.*—A 22 year old white soldier had a dry hacking cough for two years. It was accompanied by pain in the chest which gradually became more pronounced and was associated with dyspnea and palpitation after slight exertion. A definite bulge in the thoracic wall over the left precordium transmitted the heart beat but was not expansile. A roentgenogram of the chest (fig. 13) revealed great widening of the mediastinal shadow because of a mass which encroached on both the right and the left hilar lung fields. Axillary lymphadenopathy was noted, but biopsy of one of the nodes was reported to show nothing abnormal. A diagnosis of lymphoma was made, and four irradiation treatments were given, which consisted of 600 r to the anterior part of the chest and 600 r to the posterior part. Two days after the last treatment the patient became very dyspneic and cyanoic; the jugular veins were distended. A few hours later he died.

Gross Examination.—At autopsy an irregular tumor, measuring 19 by 30 by 15 cm., lay in the anterior part of the superior mediastinum, displacing the heart downward and backward. Although it encroached on both lungs and was broadly adherent to the pericardium, it did not invade any of these tissues. It was well

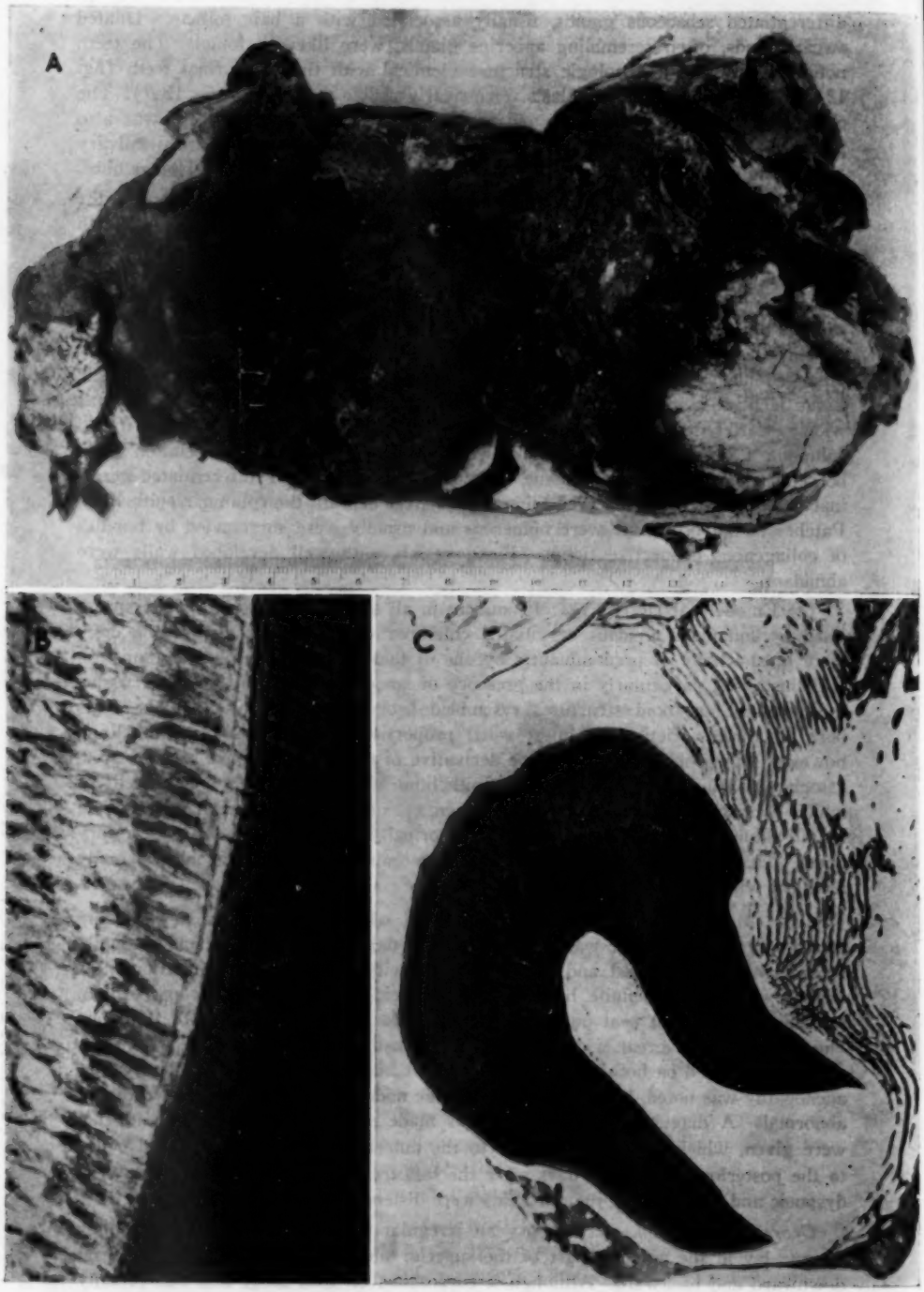

Figure 12

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encapsulated and on section presented a varied appearance. Some areas were cystic and filled with cloudy yellow fluid; other regions were made up of glistening gray tissue containing yellow areas of calcification. Large masses of friable necrotic tissue were also present.

Microscopic Examination.—(*a*) Ectodermal Derivatives: No epidermal structures could be identified; however, nerve tissue was abundant. Large masses of neuroglia were present; the astrocytes which formed the chief cellular component were large cells with polychromatic cytoplasm suggestive of that seen in astrocytoma. Associated with the glial tissue were several small circular spaces lined by tall columnar cells closely resembling ependyma (fig. 14*A*). Numerous ganglion cells were seen. One of these, isolated from the rest and not associated with neuroglia, was similar to those found in cranial or spinal nerve ganglions, being surrounded by a capsule (fig. 14*B*). A few nests of pigmented epithelial cells were present, but whether these were of ectodermal or entodermal origin could not be determined.

(*b*) Mesodermal Derivatives: A loose myxomatous connective tissue formed a stroma in which were embedded large numbers of well differentiated blood vessels and many dilated capillaries. A diffuse infiltrate of neutrophils was present in many of these areas. A few islands of hyaline cartilage were scattered through the sections; these were not associated with epithelium. A single area of membranous bone formation could be identified.

(*c*) Entodermal Derivatives: Numerous spaces were lined by tall columnar epithelial cells having a clear cytoplasm and nuclei which were directed toward the lumen rather than toward the surrounding connective tissue (fig. 14*C*). Ciliated or clearly glandular epithelium could not be found.

GROUP II. MALIGNANT TERATOMA

Death occurred in all 6 patients with cancerous teratoma, the average duration of life after the onset of symptoms being five and one-half months. The initial symptoms were similar to those of benign teratoma and consisted of pain in the chest, cough and dyspnea. In the terminal stages, compression of the large veins in the mediastinum frequently led to impairment of venous return, particularly from the head. One patient (case 14) suffered complete motor and sensory paralysis below the level of the twelfth thoracic vertebra due to metastases in that region. In 2 instances no clinical diagnosis was obtainable from the records, although the use of irradiation therapy in one suggests

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EXPLANATION OF FIGURE 12

(Case 9). *A*, cystic teratoma, which has been opened; it weighed 450 Gm. and was filled with hair and sebaceous material. On the inner surface are shown several large papillary projections covered by coarse skin from which grow long hairs. (Seven teeth arose from a piece of bone embedded in the wall; this is not shown in the figure.)

B, dentinal margin of the tooth of *B*. From left to right the figure shows the following layers: the cellular pulp, the relatively cell-free clear zone of Weil, the odontoblast layer, the poorly calcified predentin and more heavily calcified dentin. × 400.

C, tooth partly embedded in laminated cancellous bone. The enamel crown was dissolved during the preparation of the section. The radial arrangement of the dentinal tubules is clearly shown. The pulp cavity, which appears almost empty in the figure, was filled by loose connective tissue. × 6.

that a lymphoblastoma was suspected. In another case the lesion was interpreted as a benign teratoma, and in the remaining 3 cases, as a lymphoblastoma.

The youngest patient was 19 years of age; the oldest, 29 years old; the average age was 24 years, the same as for the benign teratoma group.

Cancerous change is thought to be contemporary with rapid increase in size of the benign teratoma in late adolescence and early maturity. This was well shown by Rusby,[9] who found that of 174 patients whose cases are recorded in the literature, 132 experienced symptoms first while between 10 and 40 years of age and 68 during the decade of 20 to 29 years. A satisfactory explanation of the remarkable growth of mediastinal teratoma in the young adult has not been found, although various hormonal factors have been called into account. If the

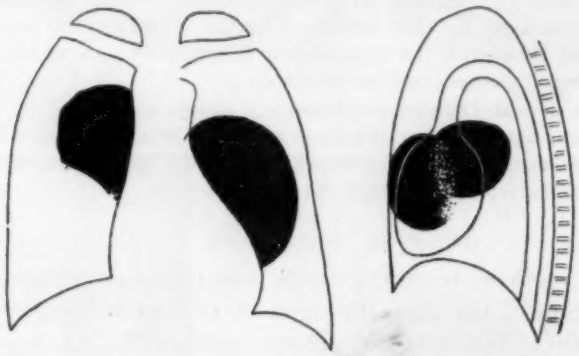

Fig. 13 (case 10).—Diagram of the widened mediastinal shadow.

mediastinal teratoma is closely linked with the thymus, as I shall later attempt to show it is, the findings of Dearth[10] on the development of the thymus in the cat are of interest. This author showed that in the 18 week old kitten, in which fat replacement of the thymic parenchyma is already well under way, corresponding to the condition of the thymus in the older adolescent or the young adult human, the thymus is decidedly more vascular than in preceding or subsequent stages. If this increased blood supply is also brought to the intimately associated teratoma, it may provide a partial explanation of the rapid growth of this tumor at that time.

CASE 11.—*Clinical Course.*—A 20 year old white soldier contracted a slight head cold in October 1940 and by Nov. 4, 1940 had a cough and some pain in the chest. Five days later he was admitted to the hospital with a diagnosis of lobar pneumonia, lower lobe of the right lung. He was given sulfapyridine after a roentgenogram showed consolidation of the entire right side of the chest (fig. 15).

10. Dearth, O. A.: Am. J. Anat. **41**:321, 1928.

Thoracentesis yielded 200 cc. of straw-colored fluid, which gave no growth on culture. The patient showed no improvement; he had a rather unproductive cough and fever. There was a loss of 20 pounds in weight during the six months before death. Bronchoscopy showed compression of the right main bronchus, interpreted as extrabronchial in origin. As the patient was in no physical condition for operation, irradiation therapy was resorted to, but it failed to decrease the size of the mass. The temperature and the pulse rate remained elevated, and the patient died with evidence of circulatory failure four months after the onset of symptoms.

Gross Examination.—At autopsy the superior mediastinum was filled by a smooth, slightly lobulated tumor that displaced the heart to the left and partly compressed the left lung. The right lung was completely atelectatic, since most of the right side of the thorax was occupied by the neoplasm. The tumor weighed 2,300 Gm., was roughly spherical and had a mean diameter of 20 cm. On section, connective tissue trabeculae extended from the capsule into the parenchyma, dividing it into lobules of varying size. Most of the tissue had a fleshy appearance and contained scattered mucin-filled cysts measuring up to 1 cm. in diameter.

The liver weighed 2,000 Gm. and showed the characteristic changes of chronic passive hyperemia. A spherical, partly necrotic tumor, 10 cm. in diameter, was found within the organ.

Microscopic Examination.—(*a*) Ectodermal Derivatives: No structures traceable to this germ layer could be identified.

(*b*) Mesodermal Derivatives: The connective tissue stroma was loose, almost myxomatous in character. Small areas of hemorrhage and necrosis were scattered throughout the sections; these were surrounded by large numbers of neutrophils. In one region were large bundles of striated muscle (fig. 16*C*); these were branched and had centrally placed nuclei; hence they may be identified as cardiac muscle. The blood vessels had poorly differentiated walls, which often consisted solely of a single layer of endothelial cells.

(*c*) Entodermal Derivatives: Many spaces were lined by ciliated columnar epithelium, but nowhere did this form a part of organoid respiratory structures. The ciliated epithelium was often abruptly replaced by tall goblet cells (fig. 16*A*), and the cyst was filled with mucin. Pleomorphic epithelial cells with one or more bizarre nuclei were present in all sections. They were found as sheets, isolated cells or cells forming irregular abortive acini. These cells were clearly cancerous and may be classified as adenocarcinoma (fig. 16*B*), but the differentiated cell from which they were derived is unknown.

The hepatic metastasis consisted of loose connective tissue, cardiac muscle and adenocarcinoma (fig. 16*D*).

CASE 12.—*Clinical Course.*—A 21 year old white man was admitted to the hospital with a history of having had cough and bloody mucoid sputum for the past three days, and chills and fever for one day. He was treated for pneumonia, improved under the regimen and was discharged. A month later he returned, complaining of cough, bloody sputum and pain in the chest; he was orthopneic and dehydrated. A roentgenogram of the chest disclosed a small effusion on the left side, associated with pneumothorax. A mass in the mediastinum infiltrated or displaced the hilar regions of both lungs (fig. 17). A diagnosis of lymphoblastoma was made and irradiation therapy administered. He died three weeks after his second admission, two months after the onset of symptoms.

Gross Examination.—At autopsy a large tumor, forming two rather discrete masses, was present in the anterior mediastinum. One mass measured 18 by 14 by 9 cm., was firm and nodular and invaded the right lung. The other mass, which

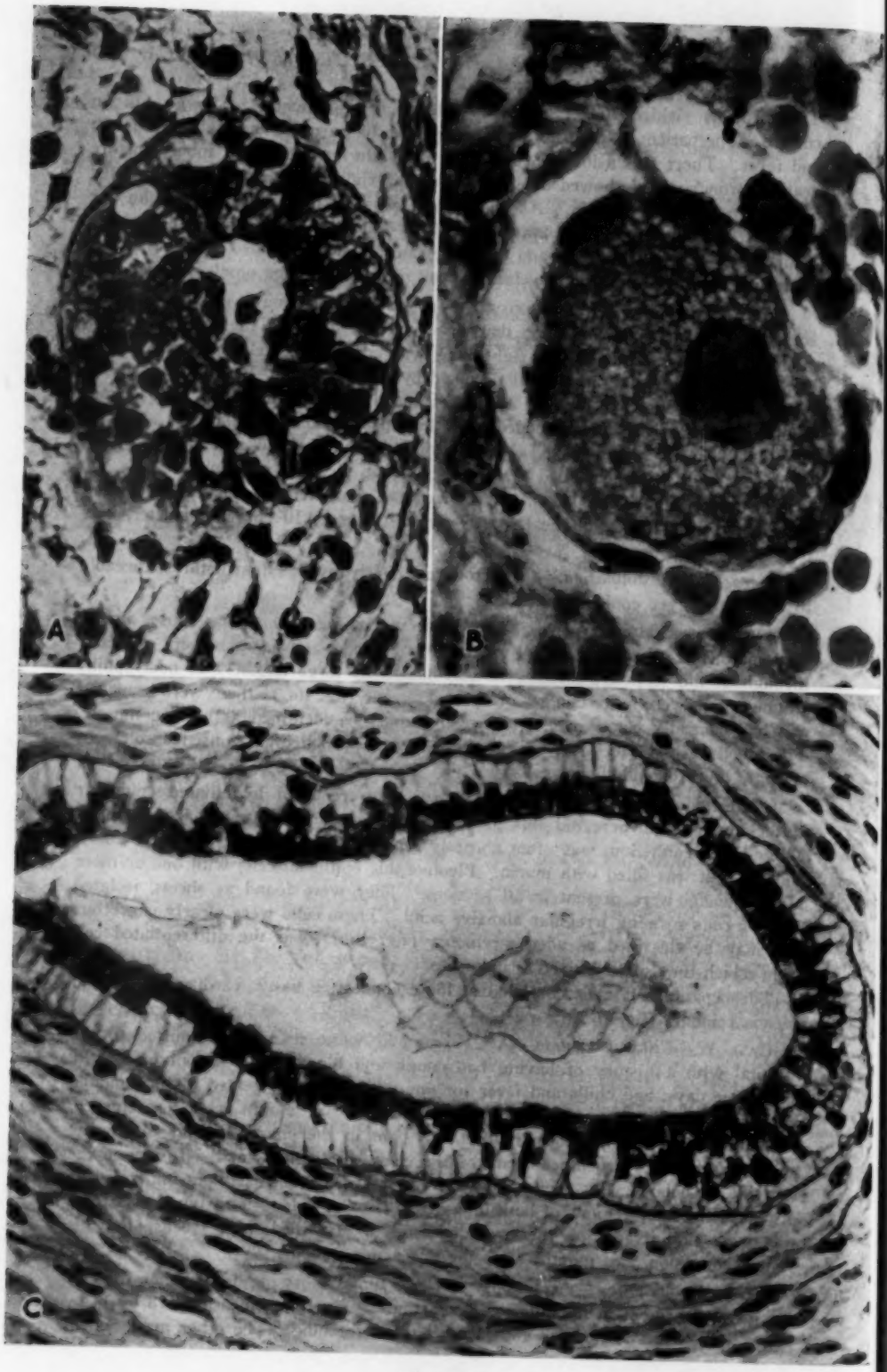

Figure 14

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measured 20 by 12 by 8 cm., was soft, friable and reddish brown. The bronchi of both lungs were clear. No distant metastases were found.

Microscopic Examination.—(*a*) Ectodermal Derivatives: Irregular small cysts were lined by stratified squamous epithelium. In none of the sections were there any organoid cutaneous structures. A few scattered collections of pigmented epithelium were present.

(*b*) Mesodermal Derivatives: The connective tissue stroma was reticulated; many of the cells were stellate; bundles of dense collagenous fibers were uncommon. Blood vessels were not numerous and, when found, had poorly developed walls. Several areas of necrosis were present; about their margins were infiltrates of degenerating neutrophils.

(*c*) Entodermal Derivatives: Alimentary and respiratory organoid structures were absent. Groups of acinous pancreatic tissue associated with islets of Langerhans and dilated ducts were numerous. Irregular masses of deeply staining epithelial cells with large vesicular nuclei were scattered throughout the sections. Histologically they had the character of cancerous epithelial cells, which in some regions were grouped into poorly formed acini; elsewhere they were wholly undifferentiated. The appearance of these cells and their relation to the pancreatic tissue suggested that the latter may have undergone cancerous change.

Case 13.—*Clinical Course.*—A 28 year old soldier was apparently well until four months before death. At that time he began to have a nonproductive cough, dyspnea, pain in the left side of the chest and an evening rise of temperature. A month after the onset of symptoms a roentgenogram of the chest revealed a mass in the mediastinum that extended into the hilus of the left lung (fig. 18). At that time a diagnosis of Hodgkin's disease was made, although mediastinal teratoma and carcinoma of the lung were also considered. The patient received irradiation therapy, 1,000 r to the anterior mediastinum and 1,000 r to the posterior mediastinum, without apparent benefit. Subsequently, another course totaling 600 r to the posterior and 2,100 r to the anterior mediastinum likewise failed to reduce the size of the lesion. All symptoms became progressively more severe, the liver became palpable, and shortly before death petechiae and ecchymoses were prominent and diffuse.

Gross Examination.—The right pleural cavity contained 500 cc. of blood-tinged fluid; the left was wholly obliterated by a tumor that had pushed the mediastinal structures into the right side of the chest. Although the superior mediastinum was filled with a mass of tumor tissue, the aorta and the esophagus were free. Except for a small portion of the apex, the left lung was completely replaced by a soft, necrotic, yellow-pink, hemorrhagic neoplasm that apparently arose in the mediastinum. On section several cystic spaces containing liquefied necrotic tissue were observed. The medial half of the upper lobe of the right lung was also invaded by the tumor. Metastatic nodules were present in the liver.

Explanation of Figure 14

(Case 10). *A*, ependyma-like structure surrounded by neuroglia. × 700.

B, ganglion cell similar to those normally found in the spinal and cranial nerve ganglions. The axon is seen leaving the cell at the top of the figure. Surrounding the cell body is a layer of sheath cells. The pale-staining polygonal cells are erythrocytes. × 1,360.

C, small cyst lined by columnar epithelium. The position of the nuclei is remarkable, being near the free surfaces of the cells rather than at their bases. The basal parts of the cells contain mucinous material. × 500.

Microscopic Examination.—(*a*) Ectodermal Derivatives: Epidermis, cutaneous appendages or nerve tissue could not be identified.

(*b*) Mesodermal Derivatives: A loose reticular network of stellate cells formed the connective tissue stroma of the tumor. Large numbers of irregular vascular spaces were present, the walls composed of a single layer of endothelium. No cartilage or bone was seen.

(*c*) Entodermal Derivatives: Irregular, poorly differentiated alveoli alternated with well formed acini lined by tall columnar epithelium, the nuclei of which were characteristically near the free surfaces rather than at the basal parts of the cells. In some regions the cells lining the alveoli were clearly cancerous and related to the large cells with polychromatic cytoplasm that were scattered throughout the sections (fig. 19*A*). The metastasis in the liver was structurally identical with the primary lesion.

CASE 14.—*Clinical Course.*—A 29 year old white soldier had no symptoms until six months before death, at which time he noted pain in the left side of the chest, radiating into the left shoulder and arm. Three weeks later dyspnea and vertigo

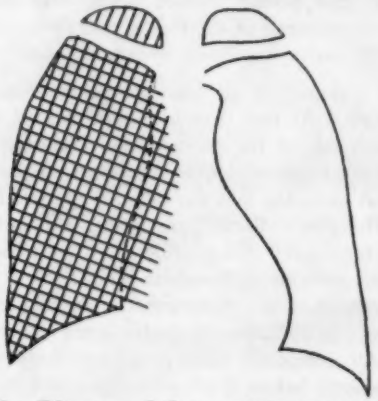

Fig. 15 (case 11).—Diagram of the roentgen appearance of the chest.

developed on exertion, symptoms which continued to occur with increasing severity until the time of death. Roentgenograms of the chest a month after the onset of symptoms showed prominence of the pulmonary artery, leading to a tentative diagnosis of aneurysm of the pulmonary artery. On the basis of subsequent roentgenologic studies, the diagnosis was changed to one of mediastinal or pulmonary tumor, probably lymphoblastoma (fig. 20). During one brief period the patient expectorated bloody sputum. A month before death there was sudden onset of excruciating pain low in the back with complete paralysis of the lower extremities. Bronchoscopy, done once, revealed narrowing of the left main bronchus but no recognizable bulging of tumor into it.

Gross Examination.—At autopsy the anterior mediastinum contained a mass, 15 by 9 by 7 cm., weighing 610 Gm. It was aherent to the pericardium and the upper lobe of the left lung but did not arise from any portion of the bronchial tree or the lung parenchyma. The cut surface of the tumor showed necrotic, gray, soft tissue with intermingling fibrous strands. The twelfth thoracic vertebral body was collapsed because of tumor growth similar to that in the mediastinum.

Microscopic Examination.—(*a*) Ectodermal Derivatives: Skin or nerve tissue could not be identified.

(*b*) Mesodermal Derivatives: The connective tissue stroma was loose, myxomatous, with only occasional bundles of collagenous fibers. Adipose tissue formed small islands that were scattered throughout the sections. There were many blood vascular spaces with walls consisting of a single layer of endothelium. Islets of developing hyaline cartilage and membranous bone were found in two sections (fig. 19*B*).

(*c*) Entodermal Derivatives: Throughout the parenchyma were irregular alveolar spaces formed by neoplastic epithelial cells, which elsewhere were grouped in amorphous masses. The cells were pleomorphic, with abundant cytoplasm and one or more large, often bizarre nuclei.

CASE 15.—*Clinical Course.*—A 19 year old white soldier was apparently well until three months before his death, at which time he experienced a dull aching pain over the left side of the chest, which did not radiate, was intermittent and was more noticeable on inspiration. About six weeks after the onset of symptoms he was admitted to the hospital with a diagnosis of pleurisy. Physical examination gave essentially negative results. A roentgenogram of the chest revealed a tumor that was interpreted as "benign dermoid cyst of the anterior superior mediastinum" (fig. 21). A therapeutic test dose of 1,800 r was given; no response was noted, and irradiation therapy was discontinued. During the last week of life the patient became drowsy and had a temperature of 101 F.

Gross Examination.—At autopsy the anterior mediastinum was occupied by a fluctuant tumor, 20 by 22 cm. It was adherent to both lungs and had infiltrated the inferior medial portion of the upper lobe of the left lung. Each pleural cavity contained approximately 1,500 cc. of blood-streaked fluid. The neoplasm surrounded the heart, completely encircling and constricting the great vessels. It filled the pericardial sac and infiltrated the epicardium. Large necrotic areas, as well as cysts filled with a mucoid substance, were encountered on section of the tumor.

Microscopic Examination.—(*a*) Ectodermal Derivatives: No structures belonging to this germ layer could be identified with certainty; atypical neuroglia might be represented. Several cystic spaces were lined by squamous epithelium, but this may be interpreted as metaplasia of mucous epithelium.

(*b*) Mesodermal Derivatives: Large numbers of poorly differentiated blood vessels were present in all sections. In the many necrotic areas the tissue was frequently flooded with erythrocytes that had escaped from the thin-walled sinuses. Polymorphonuclear leukocytes often surrounded these regions in large numbers. Several islands of young, well differentiated hyaline cartilage were present (fig. 19*C*).

(*c*) Entodermal Derivatives: In all sections of the tumor there were large pleomorphic epithelial cells with one or more bizarre nuclei. Occasionally these cancerous cells were intimately associated with alveolar structures, the columnar epithelial cells of which showed early neoplastic changes (fig. 19*D*). Irregular spaces lined by cuboidal epithelium were embedded in a loose connective tissue. Several cysts lined by goblet cells could also be identified.

CASE 16.—*Clinical Course.*—A 29 year old white soldier was apparently well until two months before death, when he had a severe cold associated with a nonproductive cough, pain in the right side of the chest and chills. Hospitalization was not necessary, and the patient apparently recovered completely. While on board ship en route to England, he became dyspneic and was confined to the ship's hospital for three days. A slight elevation of temperature was noted during his hospitalization, but he felt improved at the time of his release, although still

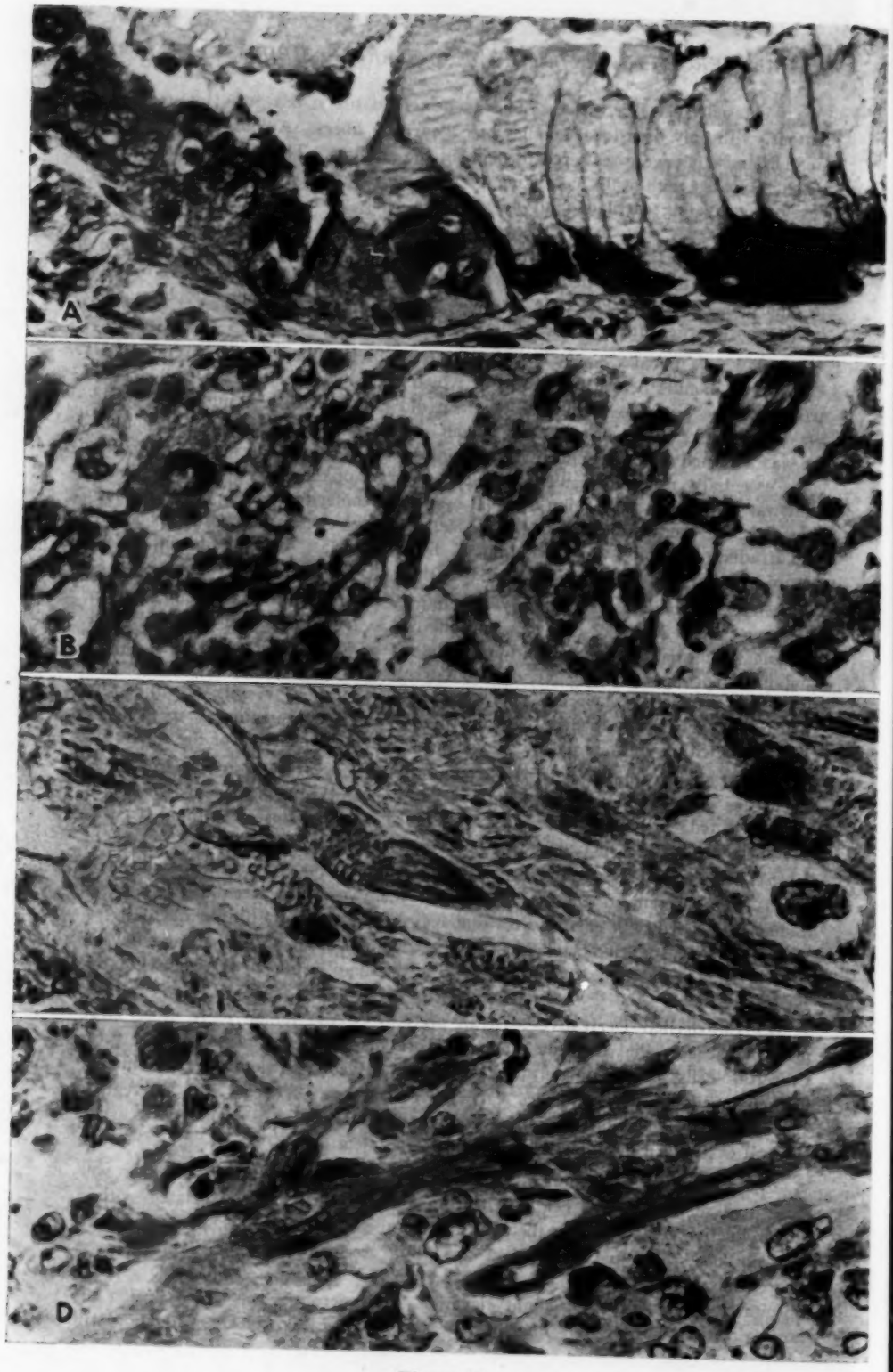

Figure 16

(See legend on opposite page)

somewhat dyspneic. On admission to an army hospital in England a week before he died, the right side of the patient's face was swollen and the veins of the neck were distended, most markedly on the right. The trachea and the heart were displaced to the left; the right side of the chest was dull to percussion, and there was bulging of the intercostal spaces. Thoracentesis yielded 500 cc. of bloody fluid. Thereafter until death, seven days later, dyspnea became more severe and was relieved only by periodic thoracic taps. On the day of death the head and neck were cyanotic, the external jugular veins were distended, and the right arm was edematous. The patient died during a venesection performed to relieve the embarrassment of the right side of the heart.

Gross Examination.—At autopsy the right thoracic cavity was filled with 3,500 cc. of bloody fluid. After removal of the fluid a large neoplasm was seen that occupied the upper two thirds of the right side of the chest and compressed the right lung. The tumor measured 16 by 11 by 8 cm., was situated just anterior to the bifurcation of the trachea and occupied most of the superior and middle portions of the anterior mediastinum. The friable mass was soft, red-gray, and well encapsulated for most of its circumference. Scattered throughout the parenchyma were gelatinous areas of degeneration. The right main stem bronchus and its branches were opened, but tumor tissue could not be demonstrated. The parietal pleura of the right side of the thorax was studded with tumor metastases. The right hilar lymph nodes and the diaphragm were likewise invaded by the neoplasm.

Microscopic Examination.—The over-all picture was one of loose cellular connective tissue, possibly cancerous, through which were scattered poorly formed acini and solid masses of neoplastic epithelial cells. The metastatic nodules on the pleura had a similar structure.

(*a*) Ectodermal Derivatives: No organoid cutaneous structures could be identified; squamous epithelium was absent. The only ectodermal derivatives that could be identified were occasional areas composed of neuroglia. Within the latter were scattered rosettes which resembled ependyma, but whether they were cannot be established with certainty.

(*b*) Mesodermal Derivatives: The connective tissue stroma varied in cellularity, but on the whole the nuclei were abundant and variable in size, with irregular shapes and staining properties similar to those seen in fibrosarcoma. The cells were stellate, and in the gelatinous regions noted grossly they resembled those of myxoma. Irregular and dilated lymph channels lent a lymphangiomatous character to some areas.

(*c*) Entodermal Derivatives: The epithelium which was sufficiently well differentiated to warrant classification resembled that of the normal intestine. In some regions the cells were grouped to form ducts and acini. In these structures the nuclei were frequently arranged along the free surfaces instead of at the

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EXPLANATION OF FIGURE 16

(Case 11). *A*, lining epithelium of a small cyst. There is an abrupt transition from tall columnar mucous cells to ciliated columnar epithelium. × 500.

B, loosely arranged cancerous epithelial cells forming no particular pattern. × 500.

C, striated muscle; in two of the fibers a centrally placed nucleus can be recognized, indicating that the muscle is of the cardiac type. × 1,360.

D, branched muscle fibers and cancerous epithelial cells in a metastatic nodule of the liver. × 500.

bases of the cells (fig. 19*E*). Much of the epithelium was frankly cancerous, forming solid clumps of cells, syncytial masses or abortive acini and ducts (fig. 19*F*).

HISTOLOGIC COMPARISON OF THE BENIGN AND THE CANCEROUS TYPE OF MEDIASTINAL TERATOMA

Benign and cancerous specimens of teratoma differ greatly in microscopic appearance. Of primary importance is the occurrence of well

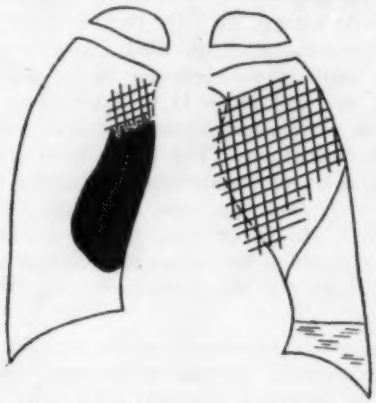

Fig. 17 (case 12).—Diagram of the roentgen shadow of a mass in the mediastinum.

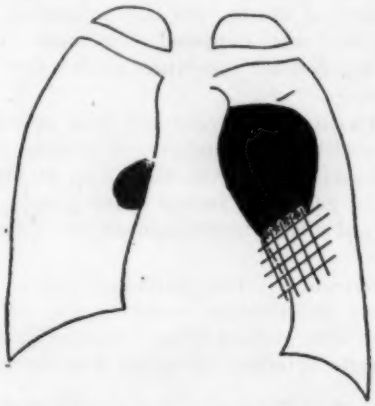

Fig. 18 (case 13).—Diagram of the roentgen shadow of a mass in the mediastinum.

differentiated structures in the benign group, few such structures being observed in the cancerous group. Recognizable ectodermal derivatives are almost completely absent in the cancerous group, whereas they are prominent in the benign. The connective tissue stroma of cancerous teratoma is usually loosely arranged, whereas that of benign teratoma is dense and of adult type. In all 6 specimens of cancerous teratoma

large areas were histologically adenocarcinoma; in none of the specimens of benign teratoma did any region resemble cancer.

STRUCTURAL COMPONENTS OF MEDIASTINAL TERATOMA AND THEIR RELATIONSHIPS

As in teratoma of other regions the structures that compose mediastinal teratoma are intermingled without apparent order. This intermingling of well differentiated tissues and organoid structures in the benign type of teratoma has repeatedly led investigators to the assumption that this type represents a malformed fetus. The problem of its genesis will be considered in the following section. Here I am concerned only with showing that experimental embryology can account for the mixture of tissues which the tumor contains. What imparts the neoplastic character to teratoma is as yet wholly unknown.

The formative interrelationship of tissues was recognized long before the concept of the organizer had been elaborated. Thus, in 1903 Beneke [11] pointed out that the manner and the rate of differentiation of connective tissue are dependent on the type and the character of the overlying epithelium. He emphasized the importance of Wilhelm Roux's *Entwicklungsmechanik* for the study of tissue relations in neoplasia. This concept was applied to teratoma by Budde,[12] who insisted that it is not permissible to identify epithelium with reference to origin on the basis of morphologic aspects alone; rather, the effect which it exercises on the underlying connective tissue must be taken into account. For example, epithelium of the intestinal type is likely to be accompanied by lymphoid tissue and smooth muscle; whereas epithelium of the respiratory type is characteristically associated with cartilage. More recently Willis [13] and Nicholson [14] have studied the morphology of teratoma from this point of view.

Under certain conditions any tissue of an embryo may act to induce in the adjacent tissue the formation of structures other than those normal to the region. As pointed out in the introduction, the agent responsible for the change may be liberated by killing the cells in boiling water. However, in the living organism less drastic processes must suffice to liberate the evocative substance. Needham [4b] emphasized the fact that under abnormal conditions the liberated evocator may induce the formation of organoid structures but never of complete organs. Hence the

11. Beneke, R.: Zur Histologie der foetalen Mamma und der gutartigen Mammatumoren, in Pathologisch-anatomische Arbeiten Herrn geh. Medicinalrath Johannes Orth zur Feier seines 25jährigen Professoren-Jubiläums, Berlin, A. Hirschwald, 1903, p. 570.

12. Budde, M.: Beitr. z. path. Anat. u. z. allg. Path. **68**:512, 1921.

13. Willis, R. A.: J. Path. & Bact. **40**:1, 1935.

14. Nicholson, G. W.: Guy's Hosp. Rep. **88**:263, 1938.

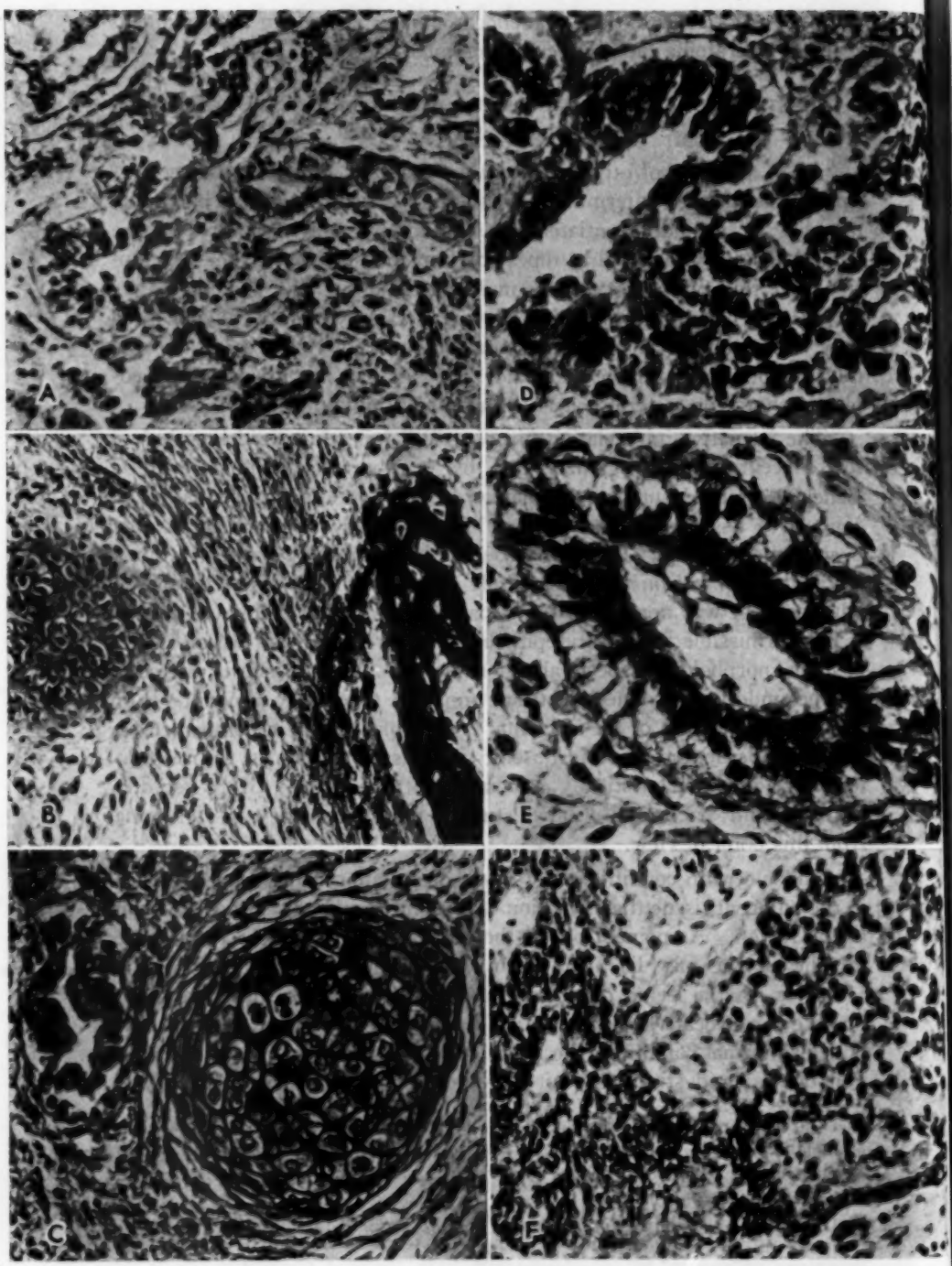

Figure 19

(See legend on opposite page)

term "evocator" rather than "organizer" in this connection. On this basis the weird hodgepodge of tissues in teratoma becomes understandable. Moreover, the conditions that bring about the liberation of the evocator may increase the capacity of the tissue to differentiate, with the formation of more varied structures during normal embryogenesis.[15]

Ectodermal Derivatives.—Nerve tissue, skin and teeth were found in all specimens of benign teratoma but in none of those of cancerous teratoma except 1 in which neuroglia and ependyma were noted. In mediastinal teratoma nerve tissue was not as prominent as it is in ovarian teratoma; only in 2 cases (6 and 10) could it be identified with certainty. In case 6 well differentiated ganglion cells were associated with neuroglia (fig. 5*C*). In case 10 neuroglia and ependyma were found in association with each other. In this case a single large ganglion cell of the type characteristic of cranial or spinal nerve ganglions (fig. 14 *B*) was discovered in a vascular area; neuroglia was absent.

Skin and its appendages were present in most of the specimens of benign teratoma and were remarkably well formed. Hair follicles preserved their normal, slightly oblique position relative to the free surface and were always accompanied by well developed sebaceous glands. These glands were usually hyperplastic, frequently assuming an almost adenomatous character (fig. 2*A*). Occasionally, groups of sebaceous glands were found unassociated with other skin derivatives. Sweat glands, often of the apocrine type, lay near the sebaceous glands; they deviated from the normal in having a more superficial position in the corium. Smooth muscles, which closely resembled arrectores pilorum, were occasionally encountered (fig. 9 *D*).

15. Rudnick, D.: J. Exper. Zool. **71**:83, 1935.

EXPLANATION OF FIGURE 19

A, cancerous epithelial cells appearing as irregular clumps or poorly formed alveoli (case 13). × 211.

B, immature hyaline cartilage and bone lamella in loose connective tissue (case 14). Loose connective tissue is characteristic of this series of cases of cancerous teratoma. × 160.5.

C, island of young cartilage in a loose connective tissue stroma (case 15). Two irregular alveoli of cancerous epithelial cells are shown in the left half of the figure. × 275.

D, cancerous epithelial cells forming a pseudoglandular acinus (case 15); many cells have separated and infiltrated the surrounding connective tissue. × 458.

E, acinous arrangement of cells that superficially resemble goblet cells (case 16). The nuclei are at the free ends rather than at the bases of the cells. The irregularity of this structure as it occurs in a cancerous teratoma is apparent when it is compared with a similar one found in a benign teratoma (fig. 14 *C*). The surrounding connective tissue is loosely arranged and cancerous in appearance. × 458.

F (case 16), another area from the same section as *E*, showing frankly cancerous epithelium arranged as solid clumps of cells and malformed acini and ducts. × 211.

Teeth were found only in case 9; the histologic relationships were entirely normal (fig. 12 *C*). The outline of the enamel crown showed that it was well developed. The dentin exhibited the normal radial striations, due to the presence of dentinal tubules. Near the bases of the teeth the characteristic palisades of odontoblasts were clearly visible (fig. 12*B*). In this connection should be cited the experiments of Huggins,

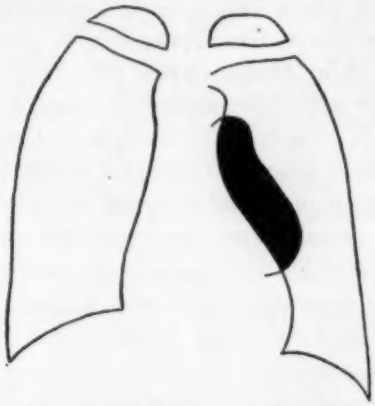

Fig. 20 (case 14).—Diagram of the roentgen shadow of a mediastinal mass.

Fig. 21 (case 15).—Diagram of the roentgen shadow of a tumor adherent to both lungs.

McCarroll and Dahlberg,[16] who found that ameloblasts of transplanted tooth germs developed normally only when in contact with odontoblasts. If this contact was lost, the cylindric character of the ameloblasts disappeared, and they formed a stratified squamous or cuboidal epithelium.

16. Huggins, C. B.; McCarroll, H. R., and Dahlberg, A. A.: J. Exper. Med. 60:199, 1934.

Mesodermal Derivatives.—These were represented by the supporting tissues—connective tissue, bone, cartilage and muscle. The connective tissue proper consisted of both collagenous bundles and elastic fibers. These were arranged about organoid epithelial structures as a tunica propria; they appeared as areolar tissue beneath the "skin" and formed a diffuse supporting stroma for the tumor parenchyma. Adipose tissue was always intimately associated with the connective tissue. Bone and cartilage were often encountered. The bone was usually of the membranous type (fig. 8 *B* and *C*) and unassociated with any other differentiated structures, but in 1 case it formed the alveolus for a tooth (fig. 12 *C*) precisely as it does in a normal jaw.

The ability of certain tissues to provoke the development of bone in adjacent areas has been well demonstrated by Huggins,[17] who used transitional epithelium of the dog's urinary bladder as organizer and rectus sheath as substrate. Such a relation of bone to epithelium was not observed in these cases of teratoma. However, a clear relationship was seen to exist between ciliated epithelium and hyaline cartilage. Rarely, islands of cartilage were found unassociated with epithelium; usually, they formed arched plaques that followed the curve of the epithelium. As noted by Huggins for bone, a thin band of connective tissue always separated the epithelium from the cartilage, preventing direct contact of the two tissues.

Hemopoietic tissue was found only in association with cancellous bone. In 1 instance it accompanied endochondral bone formation that could scarcely be distinguished from the normal (fig. 8 *A*). Lymphoid tissue was characteristically found in the "submucosa" of organoid "intestinal" structures. Just as cartilage was usually intimately related to ciliated ("respiratory") epithelium, so lymphoid tissue most often accompanied "intestinal" epithelium (fig. 2 *D*).

Smooth muscle was most often observed as longitudinal or circular bundles in organoid alimentary structures. Occasionally it was also seen in "bronchial" walls. Oblique bundles of smooth muscle passed from the "subcutaneous" tissue to the connective tissue sheaths of the hair shafts as arrectores pilorum (fig. 9 *D*). In some regions masses of interlacing bundles of smooth muscle were observed that resembled leiomyoma (fig. 8 *D*) and bore no relationship to epithelial tissues. In one section of case 11 striated muscle fibers were seen (fig. 16 *C*); these were of the cardiac type, with central nuclei and branching muscle bundles. In view of the fact that smooth muscle greatly preponderated over the striated variety in these specimens, it is interesting to note that Carey[18] was able to transform smooth

17. Huggins, C. B.: Arch. Surg. **22**:377, 1931.
18. Carey: Am. J. Anat. **29**:341, 1921.

The Structural Components and the Location of Metastases in Sixteen Cases of Mediastinal Teratoma

		Ectodermal Derivatives			Mesodermal Derivatives								Entodermal Derivatives					
	Case	Squamous Epithelium	Skin and Appendages	Nerve Tissue	Connective Tissue	Vascular Spaces	Adipose Tissue	Lymphoid Tissue	Hemopoietic Tissue	Smooth Muscle	Cartilage	Bone	Respiratory Epithelium	Intestinal Epithelium	Mucous Glands	Pancreas	Adenocarcinoma	Metatasis
Group I	1	..	+	..	+	+	+	..	..	+	+	+	+	..	+	+	..	
Benign	2	+	..	..	+	+	..	+	..	+	..	..	+	..	..	+	..	
teratoma	3	..	+	..	+	+	+	+	..	+	+	..	+	+	+	+	..	
	4	..	+	..	+	+	+	+	..	+	..	..	+	..	..	+	..	
	5	..	+	..	+	+	+	+	..	+	..	..	+	..	..	..	..	
	6	..	+	+	+	+	+	+	+	+	+	+	+	+	..	+	..	
	7	..	+	..	+	+	+	+	..	+	+	..	+	+	+	+	..	
	8	..	+	..	+	+	+	+	..	..	..	..	..	+	..	..	..	
	9	..	+ Teeth	..	+	+	+	+	..	+	+	+	+	+	..	+	..	
	10	..	..	+	+	+	+	..	..	..	+	+	..	+	..	..	..	
Group II	11	..	..	..	+	+	..	..	..	Cardiac muscle	..	..	+	+	..	..	+	Liver
Cancerous	12	+	..	..	+	+	..	..	..	..	..	..	..	..	..	+	+	
teratoma	13	..	..	..	+	+	..	..	..	..	..	..	..	..	..	..	+	Liver
	14	..	..	..	+	+	..	..	..	..	+	+	..	..	..	..	+	Vertebra
	15	..	..	..	+	+	..	..	..	..	+	..	..	..	..	..	+	
	16	..	..	+	+	+	..	..	..	..	..	..	..	+	..	..	+	Lymph node

muscle of the urinary bladder into striated muscle of the myocardial type by forcing it to undergo rhythmic contractions.

Entodermal Derivatives.—These include "intestinal" and "respiratory" structures and pancreas. The manner in which these epithelia reacted to supporting mesodermal structures has been discussed in the preceding section. Their interrelations were frequently intimate, and transition from one type of epithelium to the other was often abrupt (figs. 5*B* and 16*A*). An explanation of this intimate association is furnished by the experiments of Rudnick.[19] This investigator transplanted the lung primordia, including the adjacent gut wall and splanchnic mesoderm, of the 3 day chick embryo to the chorioallantoic membrane of the hen's egg. Parts of the entoderm which normally were not destined to take part in the formation of the respiratory tract showed a marked tendency to form respiratory structures. Occasionally both respiratory and intestinal epithelium lined the same tube, and one type of epithelium was frequently found to merge into the other. In another experiment Rudnick and Rawles[20] obtained complexes, lined by cells resembling intestinal epithelium and surrounded by smooth muscle, in grafts which originally contained no entoderm. From this they concluded that epithelia from other germ layers may not only take on a form characteristic of intestinal lining but may be associated with connective tissue and muscle to simulate alimentary structures. These experiments should serve as a warning against the too facile identification of structures found in teratoma.

One of the most surprising observations made in this group of specimens of benign teratoma was the frequency of well differentiated pancreas. Pancreas was observed as large, readily identifiable masses in 6 of the 10 specimens; in 5 of these, islets of Langerhans were associated with the acinous tissue (figs. 2*B* and 5*A*). Pancreatic tissue may have been seen in a seventh instance, case 2, but could not be identified with certainty. In 1 instance of cancerous teratoma (case 12) pancreas with islets was likewise present. In most instances the acinous cells, islets and ducts were so well differentiated and in such harmonious relationship that they could not be distinguished from those of normal pancreas. The high incidence of pancreas in these specimens of mediastinal teratoma as compared with its infrequent occurrence in those of teratoma of the gonads and other sites, may aid in determining the site from which teratoma takes its origin. This will be considered further in the section on the genesis of teratoma. It should, however, be noted that the literature contains few references to pancreatic tissue in mediastinal teratoma. The cases of Irene

19. Rudnick, D.: J. Exper. Zool. **66**:125, 1933.

20. Rudnick, D., and Rawles, M. E.: Physiol. Zool. **10**:381, 1937.

Gordon [21] and Hablützel [22] are the only ones listed by Rusby; another was reported by Harrington.[23]

GENESIS OF TERATOMA

For centuries teratoma has been a cause of wonder and superstition. In times past, according to Gould and Pyle,[24] teratoma in the male was regarded as a repetition of the process by which Eve was born of Adam. The finding of ovarian teratoma in the body of a young woman was considered as conclusive proof that she had been unchaste. With the development of embryology and teratology during the first half of the nineteenth century, cases of teratoma were classified into two main groups: (1) ovarian and testicular teratoma, which were believed to arise spontaneously from germ cells by a process of parthenogenesis, and (2) all other cases of teratoma, in which the finding was regarded as an included twin—that is to say, as a "fetus in fetu." Both of these hypotheses, now well over a century old, are still widely accepted.

Hypothesis of Fetus in Fetu.—In a long series of articles Nicholson carefully analyzed teratomatous specimens of the most varied origin and structure. In none was he able to find any evidence of fetiformity. In reviewing cases described by earlier investigators as instances of abortive fetus he was repeatedly able to show that the limbs, head, and "well developed organs" reported by these observers were actually the product of a too vivid imagination. In his characteristic style he wrote [25]: "Since it is an amiable weakness of teratology to fancy that the words similarity and identity are synonymous, we readily see in a horrid tumor a smiling babe." Willis,[13] in a paper that is one of the outstanding contributions to teratology, listed the following reasons for concluding that teratoma is not a distorted fetus: (1) with extremely rare and doubtful exceptions, teratoma exhibits no signs whatever of axiation, metameric segmentation or delamination of germ layers; (2) teratoma possesses no organs or true somatic regions; (3) teratoma frequently contains a multiplicity of certain constituents, e. g., dozens of "tonsils," many separate embryonic "nervous systems"; (4) teratoma characteristically shows an anomalous absence of vital tissues; (5) abnormal tissue relationships and mixtures are frequent in specimens of teratoma.

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21. Gordon, I.: Frankfurt. Ztschr. f. Path. **40**:224, 1930.
22. Hablützel, C.: Schweiz. med. Wchnschr. **63**:1308, 1933.
23. Harrington, S. W.: J. Thoracic Surg. **1**:663, 1932.
24. Gould, G. M., and Pyle, W. L.: Anomalies and Curiosities of Medicine, Philadelphia, W. B. Saunders Company, 1897.
25. Nicholson, G. W.: Guy's Hosp. Rep. **84**:389, 1934.

Germ Cell Hypothesis.—By demonstrating that teratoma is not a malformed fetus, the hypothesis of fetus in fetu is disposed of. But the problem of a so-called parthenogenetic development of the germ cells in the gonads is not so easily handled. The work of Jacques Loeb and of many investigators following him has conclusively proved that the vertebrate egg cell can begin development after application of stimuli other than that of sperm entry. In a long monograph Bosaeus [26] showed that frogs' eggs induced to develop parthenogenetically and then placed into the celomic cavity of the parent frog produced masses resembling in general structure human ovarian teratoma. More recently Greene [27] succeeded in transplanting rabbit embryos, either in whole or in part, to the anterior chambers of the eyes and to the testicles of rabbits or guinea pigs. He obtained growths which resembled teratoma and which could be transferred serially. On the basis of Greene's work it may be argued that Bosaeus has merely demonstrated the ability of embryonic tissue to survive and differentiate for a time under abnormal circumstances. However, some evidence favoring the germ cell hypothesis has been obtained through the recent experimental production of testicular teratoma.

In 1926 Michalowsky,[28] and after him Falin [29] and Bagg,[30] produced teratoma in the testis of the rooster by injecting 0.3 cc. of a 5 per cent solution of zinc chloride. Efforts to produce teratoma in extragonadal tissues by this method have failed.[31] The cells that give origin to teratoma have not been specifically identified; Falin has regarded them as pluripotential testicular cells. That they may well be primitive germ cells is indicated by the fact that teratoma arises only following an injection made during the spring months when spermatogenesis is most active and that teratoma cannot be induced in the immature testis. Falin expressed the belief that an important role is played by the focal necrosis resulting from the injection of the zinc compound. He considers it likely that the death and disintegration of cellular elements liberate evocators which act on testicular cells. This explanation is supported by the results which Holtfreter obtained after transplanting bits of boiled tissue into the amphibian blastocele.[6]

In view of these findings it appears probable that teratoma of the testes or the ovaries arises from pluripotent germ cells normally present in these organs. A sharp distinction must be drawn, however, between

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26. Bosaeus, W.: Beiträge zur Kenntnis der Genese der Ovarial-embryone, Uppsala, Almqvist & Wiksells, 1926.

27. Greene, H. S. N.: Cancer Research **3**:809, 1943.

28. Michalowsky, I.: Centralbl. f. allg. Path. u. path. Anat. **38**:585, 1926.

29. Falin, L. I.: Am. J. Cancer **38**:199, 1940.

30. Bagg, H. J.: Am. J. Cancer **26**:69, 1936.

31. Bischoff, F.; Long, M. L., and Rupp, J. J.: Am. J. Cancer **38**:404, 1940.

the pluripotent precursors of the germ cells and the mature germ cells themselves. The primitive pluripotent germ cells, which eventually become egg cells or sperm, are not such as these at the time of inception of teratoma. The egg cell is not undifferentiated; rather it is a highly specialized cell which when fertilized reacts by producing an embryo—not a teratoma. Experimental parthenogenesis likewise invariably produces a recognizable embryo, not a tumor. In the case of the mature sperm the impossibility of even parthenogenetic development, much less tumor formation, is obvious.

Hypothesis of Extragonadal Germ Cells.—That the primordial germ cells of the developing embryo do not arise in the gonads has been accepted for many years. Where then do they come from? In 1870 Waldeyer suggested that they originate in a differentiated portion of the celomic epithelium that covers the urogenital folds. Subsequent work has indicated that this region is only the last way station of a much more extended journey. In 1914 Swift [32] demonstrated that the primordial germ cells of the chick embryo arise in a crescent-shaped region of germ wall entoderm at the anterior margin of the area pellucida. At first these cells are in the space between entoderm and ectoderm; with the appearance of the mesoderm they enter this layer and the developing blood vessels within it. Early in their course they migrate by ameboid movement, but subsequently they are carried in the blood stream to all parts of the embryo. Later the primordial germ cells become more numerous in the vessels of the splanchnic mesoderm. They continue to accumulate in the radix mesenterii and the celomic epithelium on both sides of the celomic angle; elsewhere they degenerate and disappear. Those in the celomic epithelium remain there until the formation of the gonad begins, when they gradually pass into that organ. This concept of a germ pathway or *Keimbahn* has been supported by numerous investigations, among them those of Reagan [33] and, more recently, of Dantschakoff.[34]

With this in mind it is interesting to consider the 11 cases of spontaneous teratoma of the chicken collected from the literature by Mashar [35] and supplemented by 2 additional cases of his own. In 5 cases the tumor originated within or on the surface of a kidney; in 3 a testicle was the primary site; in 1 case the tumor was found in an ovary, in 1 case in the mesentery and in 1 case in the abdominal air sac; in 2 cases the location was not given. These sites accord well with the regions of greatest accumulation of the primordial germ

32. Swift, C. H.: Am. J. Anat. **15**:483, 1914.

33. Reagan, F. P.: Anat. Rec. **11**:251, 1916-1917.

34. Dantschakoff, W.; Dantschakoff, W., Jr., and Bereskina, L.: Ztschr. f. Zellforsch. u. mikr. Anat. **14**:323, 1932.

35. Mashar, U.: Virchows Arch. f. path. Anat. **285**:155, 1932.

cells. The record of only a single case of ovarian teratoma is probably related to the fact that only 1 hen was included in the series.

To what extent primordial germ cells arrested in an extragonadal position may account for extragonadal teratoma of man is problematic. In the mouse embryo Everett [36] found primordial sex cells first in the gut entoderm, whence they migrated into the splanchnic mesenchyme and through the dorsal mesentery into the genital ridge. One might therefore expect the highest incidence of extragonadal teratoma to be within the intestinal wall and the mesentery. But this is not the case; however, a few cases of teratoma occurring in these regions have been reported. It is possible that teratoma of these and of retroperitoneal sites arise from "undescended" primordial cells, much as teratoma of the testis or the ovary originate from these cells after they have reached the gonads. Sacral and anterior mediastinal teratoma, however, are not accounted for by this hypothesis.

Hypothesis of Fertilized Polar Bodies.—Although still laboring under the mistaken belief in the fetal character of extragonadal teratoma, some investigators became dissatisfied with the "included twin" hypothesis. At the time when studies of the maturation of the egg cell were occupying the attention of embryologists, Marchand [37] and Bonnet [38] suggested that the polar bodies of the developing egg may be fertilized and pass into the medullary groove or other fissure, there to grow and differentiate into teratoma. After it was shown that polar bodies could not be stimulated to further development, this idea was dropped.

Hypothesis of Displaced Blastomeres.—With the discovery that the individual blastomeres up to and including the eight cell stage can each form a complete embryo, the scene was set for a new hypothesis. During the past fifty years the misplaced blastomere has been frequently called on to account for the presence of teratoma in various parts of the body.[39] The reasoning here is faulty because the early blastomeres can go on to independent development only if they are separated from the organizing influence of the adjacent cells. It has been shown experimentally that a translocation of embryonic cells while they are still topipotent, i. e., in the blastular stage, will result in their developing in conformity with the new environment. The problem may be approached from another angle. If two fertilized but yet uncleaved eggs of the salamander are united, they will form not conjoined twins but a single giant embryo. This demonstrates how great is the organiz-

36. Everett, N. B.: J. Exper. Zool. **92**:49, 1943.

37. Marchand, F.: Mediastinal Geschwülste, in Eulenburg, A.: Real-Encyclopädie der gesamten Heilkunde, Vienna, Urban & Schwarzenberg, 1897, vol. 15.

38. Bonnet, M.: Ergebn. d. Anat. u. Entwcklngsgesch. **9**:820, 1899.

39. Smith, L. W., and Stone, J. S.: Ann. Surg. **79**:687, 1924.

ing capacity of the early embryo—precisely the stage at which its failure has been postulated in the concept of a misplaced blastomere. Similar experiments on isolated blastomeres and fused eggs of rats have recently been carried out by Nicholas and Hall [40]; the results were identical with those reported for the salamander.

The Morphogenetic Hypothesis.—The attempt to explain the extragonadal appearance of teratoma on the basis of the misplaced totipotent cell has recently been revived by the application of the "morphogenetic theory" of Holmdahl.[41] This author amplified the work of Keibel, who first called attention to the fact that the tail and posterior segments of the trunk of the chick arise from an indifferent cell mass, the "tail-trunk bud" (*Rumpfschwanzknopse*). In addition to the posterior portion of the trunk, a narrow median region of the body also arises directly from the undifferentiated cell mass found in the dorsal blastopore lip (amphibian) or the anterior end of the primitive streak (chick and man). Holmdahl expressed the belief that the notochord, the underlying entoderm which forms the gut, and the basal portion of the neural groove differentiate directly from this tissue; they do not first pass through a germ layer stage. A number of other investigators, among them Vogt, Kingsbury [42] and Peter,[43] are in essential agreement with this hypothesis. The Belgian embryologist Pasteels [44] is one of its leading opponents.

Holmdahl has applied his hypothesis to the origin of teratoma,[45] placing special emphasis on the cases in which it arises in the sacral and the anterior mediastinal region. But dislocation of the totipotent cells should occur with approximately equal frequency throughout the mass of undifferentiated cells. His hypothesis therefore fails to account for the relatively high incidence of teratoma in the mediastinal and sacral regions. Moreover, since the indifferent cell mass is dorsal in position, the sacral location of teratoma can readily be explained but not the mediastinal, which is anterior to the heart. Nevertheless, further developments in this non-germ-layer hypothesis of the morphogenesis of the axial and caudal areas of the embryo will be followed with interest. When fully evaluated, it may form a useful part of the oldest and most widely applicable hypothesis of the genesis of extragonadal teratoma, namely, that it is due to a dislocation of tissues during early embryogenesis.

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40. Nicholas, J. S., and Hall, B. V.: J. Exper. Zool. **90**:441, 1942.

41. Holmdahl, D. E.: Anat. Anz. (supp.) **88**:127, 1939. Holmdahl, D. E.: Arch. f. Entwcklngsmechn. d. Organ **139**:191, 1939.

42. Kingsbury, B. F.: J. Comp. Neurol. **56**:431, 1932.

43. Peter K.: Ztschr. f. mikr.-anat. Forsch. **36**:378, 1934.

44. Pasteels, J.: Arch. de biol., Paris **48**:381, 1937.

45. Holmdahl, D. E.: Acta path. et microbiol. Scandinav. **19**:603, 1942.

The Hypothesis of Tissue Dislocation with Liberation of Organizers.—Since the days of von Baer, embryologists have marveled at the complexity of the invaginations, delaminations and migrations of cell groups during embryogenesis. Small wonder that bits of tissue may be misplaced, particularly in regions where these processes are intricate! Because the most elaborate movements of cell groups occur only after the definitive germ layers have been formed, when these displaced tissues are no longer totipotent, many investigators were loath to seek in them the origin of such a complex malformation as teratoma. Readily, however, did they ascribe to tissue dislocations such less complex developmental faults as craniopharyngioma, sacral spina bifida and pilonidal cyst, branchial sinus, branchial fistula and mediastinal cyst.

As was detailed in the foregoing pages, experimental embryology has demonstrated the capacity of tissues to differentiate in directions other than that normally expressed during embryogenesis. Not only is a dislocated tissue subjected to the action of the organizers of its new environment, but its capacity to react to them may be altered. As a result, it may differentiate into structures that are wholly foreign to that region. In areas where dislocation of tissues may involve all three germ layers teratoma is often found. This concept may explain the genesis of extragonadal teratoma in most instances.

Genesis of Sacral Teratoma.—On the basis of his embryologic researches, Holtfreter [46] has associated human sacral teratoma with faulty gastrulation resulting in a mass of entomesoderm being attached near the caudal end of the entodermal tube. Experimentally Holtfreter [47] produced this abnormality by cultivating the blastulas of newts in a 0.35 per cent salt solution (Ringer's solution). In amphibians neither skin nor nerve tissue is found in these masses, which do not come in contact with ectoderm. However, in man, in whom gastrulation is considerably modified, contact of the entomesoderm with ectoderm occurs, and neural tissue is induced in the latter by the organizer activity of the underlying mesoderm.

GENESIS OF TERATOMA OF THE ANTERIOR MEDIASTINUM

Through the years, two hypotheses of the genesis of teratoma of the anterior mediastinum have had alternating popularity: (*a*) It is due to a disturbance of the development of the branchial clefts; (*b*) it is an included twin. During the greater part of the nineteenth century most cases of teratoma of the anterior mediastinum reported were examples of the cystic variety consisting almost solely of skin and its

46. Holtfreter, J.: Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. **42**:78, 1933.

47. Holtfreter, J.: Arch. f. Entwcklngsmechen. d. Organ **129**:669, 1933.

appendages. Pinders,[48] Pflanz,[49] Virchow[50] and Wilms[51] considered teratoma of this type to be derived from the branchial cleft. Collenberg,[52] because he found thyroid tissue in his case, implicated this organ. Marchand[53] found the thymus gland intimately associated with teratoma of the mediastinum in the case studied by him and therefore sought the origin of the growth in the thymus, suggesting a possible derivation from the corpuscles of Hassall.

In 1898 Ekehorn[54] reported 2 cases in which tissues of all three germ layers were readily demonstrated. He expressed the belief that such complex structure could not be explained on the basis of disturbed embryogenesis; instead he interpreted it as evidence of an included twin and similarly accounted for the complexity of specimens reported by previous authors. Among these was the first specimen of mediastinal teratoma to be recorded. This, reported by Gordon[55] in 1823, was remarkable for the possession of well developed teeth embedded in alveolar bone, which Ekehorn identified as a jaw. Askanazy[56] lent the weight of his authority to the theory of fetus in fetu, accounting for the presence of the included twin by assuming that a totipotent germ cell passed into the celomic cavity during early fetal life. Hattori[57] reported a case of teratoma wholly embedded in the thymus gland; he offered the intriguing suggestion that an ovum or a blastomere had passed into the third branchial pouch and from there wandered into the deeper portions of the mediastinum. In 1932 Harrington[23] reported a tumor of the anterior mediastinum which "represents the caudal portion of a parasitic fetus."

It has now become clear that the hair-containing cyst (dermoid) of the mediastinum is linked with the more complex teratoma by numerous intermediate forms and that all forms must be genetically similar. The fetal character of teratoma of the mediastinal and other sites has been disproved, and an origin within the branchial cleft appears more likely. The frequency of developmental faults in this region is indicated by the common occurrence of branchial fistula and sinus, often associated with small tabs of cartilage.

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48. Pinders, W.: Ueber Dermoidcysten des vorderen Mediastinums, Inaug. Dissert., Bonn, J. Bach, Wwe., 1887; cited by Rusby.[9]

49. Pflanz, E.: Ztschr. f. Heilk. **17**:473, 1896.

50. Virchow, R.: Virchows Arch. f. path. Anat. **53**:444, 1871.

51. Wilms, M.: Deutsches Arch. f. klin. Med. **55**:289, 1895.

52. Collenberg, T.: Zur Entwickelung der Dermoidkystome, Inaug. Dissert., Breslau, F. W. Jungfer, 1869.

53. Marchand, F.: Ber. d. oberhess. Gesellsch. f. Nat. u. Heilk. **22**:325, 1833.

54. Ekehorn, G.: Arch. f. klin. Chir. **56**:107, 1898.

55. Gordon, J. A.: Med.-Chir. Tr. **13**:12, 1825.

56. Askanazy, M.: Verhandl. d. deutsch. path. Gesellsch. **11**:39, 1907.

57. Hattori, S.: Verhandl. d. jap. path. Gesellsch. **3**:130, 1913.

Teratoma of the mediastinum always occupies the region of the thymus gland and has been frequently found in intimate relation with this structure.[58] Schmincke[59] described a cherry-sized cyst in the lower left lobe of the thymus in a 31 year old woman; it was lined by "skin" and filled with hair and sebaceous material. In the 16 cases reported in the present series thymic tissue was found within the capsule in 4 instances; however, it must be emphasized that sometimes only portions of the teratoma were available for detailed microscopic study. An additional case, not included in the series, is that in which teratoma completely replaced the thymus of a 10 day old infant. No thymic tissue was found elsewhere. On histologic examination this growth was seen to contain well differentiated nerve tissues.[60]

Of all the branchiogenic structures, the thymus anlage is the most plausible site for the development of mediastinal teratoma. The thymus is the only branchiogenic organ that regularly descends into the anterior mediastinum. During the embryogenesis of the thymus there is intimate association of ectoderm and entoderm, accompanied by mesenchyme.

In man, most of the thymus is derived from the third entodermal pouch of the pharynx (fig. 22). The role of ectoderm in the formation of the thymus has been disputed. It is pertinent to the morphogenesis of mediastinal teratoma to consider this point. The third branchial cleft, an ectodermal derivative, opens onto the surface of the skin through the cervical sinus and becomes dilated at its distal end to form the cervical vesicle. Subsequently, the latter severs its cutaneous connection but remains in close contact with the third pharyngeal pouch. Thereafter, according to Weller[61] and other investigators, the cervical vesicle slowly degenerates and disappears, forming no part of the definitive thymus. Recently, however, Norris[62] reinvestigated the fate of the cervical vesicle in detail and found that it spreads over the surface of the entodermal thymus, forming an ectodermal cortical layer. Some of the ectodermal cells become disengaged and are displaced into the medulla by swarms of lymphocytes that are

58. Cordes: Virchows Arch. f. path. Anat. **16**:290, 1859. Rolleston, H. D.: J. Path. & Bact. **4**:228, 1897. Rénon, Delille, and Nandrot: Bull. et mém. Soc. anat. de Paris **82**:308, 1907. Schuster, H.: Beitr. z. path. Anat. u. z. allg. Path. **75**:403, 1926. Wolfsohn, G.: Arch. f. klin. Chir. **155**:680, 1929. Rose, E.: M. Clin. North America **14**:999, 1931. Struthers, R. R.: Canad. M. A. J. **26**:68, 1932. Marchand.[53] Hattori.[57]

59. Schmincke, A.: Pathologie des Thymus, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, pp. 760-809.

60. This case was made available to me by Major E. D. Peasley.

61. Weller, G. L., Jr.: Contrib. Embryol. **24**:93, 1933.

62. Norris, E. H.: Contrib. Embryol. **27**:191, 1938.

crowding into the cortex. The isolated ectodermal cells are at first recognizable by their large size and vesicular nuclei; subsequently, they form Hassall's corpuscles.

If Norris' conception of the origin of Hassall's corpuscles is correct, the thymus has the unique arrangement of ectodermal cells within a cell mass derived from entoderm. However, even if Hassall's corpuscles are entodermal in origin, it cannot be denied that the entodermal thymus at one stage in its development lies in intimate contact with the ectodermal cervical vesicle. The embryogenetic fault preceding the formation of teratoma may then consist of failure on the part of the cervical vesicle to disappear.

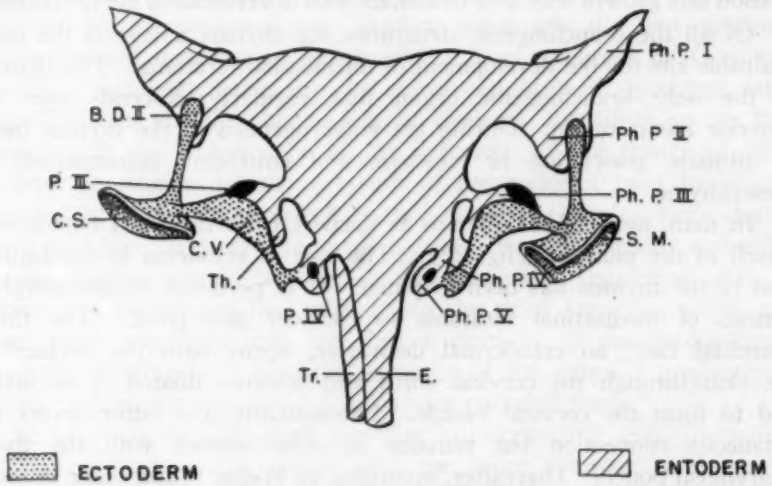

Fig. 22.—Diagram showing the pharyngeal pouches and their relation to the branchial clefts in a 6 week (12 mm.) human embryo, viewed from the dorsal aspect. *B. D.* II indicates branchial duct II; *C. S.*, the cervical sinus; *C. V.*, the cervical vesicle; *E*, the esophagus; *P.* III and *P.* IV, parathyroid glands III and IV; *Ph. P.* I to V, pharyngeal pouches I to V; *S. M.*, the orifice of the sinus; *Th.*, the entodermal anlage of the thymus; *Tr.*, the trachea. (After Hammar, J. A.: Zur gröberen Morphologie und Morphogenie der Menschenthymus, Anat. Hefte **43**: 201, 1911).

Partial degeneration of the cervical vesicle or of Hassall's corpuscles releases organizers (compare areas of necrosis as inductors of experimental testicular teratoma or boiled tissue as evocators) that act on the embryonic entodermal cells and the surrounding ectoderm. The capacity of even adult thymic reticulum cells to respond in this manner is shown by the occurrence of ciliated epithelium about the areas of necrosis which are frequently found in the dog's thymus.[63]

63. Bargmann, W.: Der Thymus, in Möllendorf, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1943, pp. 1-172.

With reference to the presence of nerve tissue in teratoma of the thymus it may be noted that Politzer and Hann [64] observed in the early embryo an intimate relation between the cervical sinus and the ganglion nodosum of the vagus. This intimate connection was further emphasized by Kolmer,[65] who expressed the belief that some of the nerve cells in the ganglion nodosum may actually be derived from epithelium of the branchial cleft. Gilmour [66] has lately described an accessory left parathyroid gland III embedded in the ganglion of the trunk of the left vagus. No capsule separated it from the nerve tissue. Since parathyroid gland III arises from the third pharyngeal pouch together with the thymus (fig. 22), the report of Gilmour lends support to the belief that some of the nerve cells of the ganglion nodosum are derived from the cervical vesicle.

It seems probable that the site of origin determines the types of tissue which comprise teratoma. Thus, entodermal derivatives may be expected to be prominent in thymic teratoma. This is actually the case in the 10 specimens of benign teratoma of the present series. Bronchial and intestinal organoid structures are common, but of particular significance is the presence of well differentiated pancreas in 6 or possibly 7 specimens. On the other hand, in 30 specimens of ovarian teratoma examined by me, not once was pancreatic tissue observed. Similarly in 150 specimens of teratoma of the testis recently studied by another member of the staff, no pancreas was identified. Aberrant pancreas is not infrequently found throughout the gastrointestinal tract.[67] Lauche [68] stated that the entire foregut possesses the latent capacity to form pancreas. Therefore, the frequent presence of pancreas in specimens of teratoma of the anterior mediastinum may be ascribed to the important role played by part of the foregut, the third pharyngeal pouch, in their genesis.

One may conclude that teratoma of the anterior mediastinum has its origin in faulty embryogenesis of the thymus. Teratoma of this region may therefore be identified more precisely as teratoma of the thymus.

SUMMARY

The clinical course and morphologic characteristics of teratoma have been studied in 16 instances in which the growth occupied the anterior

64. Politzer, G., and Hann, F.: Ztschr. f. Anat. u. Entwcklngsgesch. **104**:670, 1935.

65. Kolmer, W.: Ztschr. f. Anat. u. Entwcklngsgesch. **87**:354, 1928.

66. Gilmour, J. R.: J. Path. & Bact. **52**:213, 1941.

67. Faust, D. B., and Mudgett, C. S.: Ann. Int. Med. **14**:717, 1940. Troll, M. M.: Arch. Path. **38**:375, 1944.

68. Lauche, A.: Virchows Arch. f. path. Anat. **252**:39, 1924.

mediastinum. In 10 of these cases the growth was benign and in 6 cancerous. All the patients fell within the military age group of 18 to 38 years; 15 were males; 1 was a female.

In the specimens of benign teratoma the most frequently encountered organoid structures were skin, "intestine," "bronchus" and "pancreas." The incidence of well developed pancreas in 6 of the 10 specimens is remarkable in view of its infrequent occurrence in specimens of teratoma of other regions.

The specimens of cancerous teratoma of this series were characterized by almost complete absence of ectodermal derivatives, such as skin or nerve tissue. The connective tissue was loose and cellular and may have undergone cancerous change. The cancerous epithelium was arranged as adenocarcinoma in each instance. Well differentiated organoid epithelial structures were absent. Metastases were found in 4 cases.

During the past half century the experimental analysis of morphogenesis has made important advances. Outstanding among these has been the development of the concept of the organizer which holds that substances ("organizers") liberated by one group of cells may determine the differentiation and the organization of other groups of cells.

The hypotheses of the genesis of teratoma have been examined in the light of advances in embryology. It is concluded that teratoma of the ovaries and the testes is due to abnormal growth and differentiation of undifferentiated precursors of the germ cells. Extragonadal teratoma, however, is the result of a local dislocation of tissues during embryogenesis.

Teratoma of the anterior mediastinum probably arises from tissue dislocations in the anlage of the thymus.

Case Reports

STRUMA OVARII

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THAT thyroid tissue occurs within the ovary has long been recognized. It occurs relatively frequently in association with dermoid cysts of that organ. Wynne, McCartney and McClendon,[1] in an analysis of 198 cases of ovarian teratoma and dermoid cysts reported in the literature, recorded thyroid tissue as present in 11.6 per cent. Koucky [2] reported an incidence of 19 per cent in 100 cases of ovarian dermoids. The total amount of thyroid tissue and the percentage relative to other tissue components vary within wide limits. The thyroid element may represent merely an incidental microscopic observation, or it may form a sizable portion of the ovarian mass, overshadowing the associated dermoid elements. The term "struma ovarii" has been applied when the thyroid component has formed a significantly large part of the tumor. Rarely, an ovarian tumor composed entirely of thyroid tissue is observed. Such a tumor might well be designated as pure struma ovarii. In an analysis of 50 cases of struma ovarii reported in the literature, Frankel and Lederer [3] noted 11 in which thyroid tissue formed the entire tumor. They reported 1 additional case of pure struma ovarii. Since then we have encountered reports of 15 other cases which we accept as instances of pure struma ovarii.[4] The data supplied in some reports are not sufficiently inclusive to establish the absence of other tissue components in the lesion. The publication of Dionisi and Ferraris [5] was not accessible to us. To the group of cases of pure struma we add case 1 in the following report:

From the Department of Pathology, University of Pittsburgh, and the Presbyterian and Woman's Hospitals.

1. Wynne, H. M. N.; McCartney, J. S., and McClendon, J. F.: Am. J. Obst. & Gynec. **39**:263, 1940.

2. Koucky, J. D.: Ann. Surg. **81**:821, 1925.

3. Frankel, J. M., and Lederer, M.: Am. J. Obst. & Gynec. **16**:367, 1928.

4. (*a*) Brown, A. L., and Shoor, M.: Am. J. Surg. **55**:173, 1942. (*b*) Wynne, McCartney and McClendon.[1] (*c*) Lyday, R. O.: Am. J. Surg. **25**:89, 1934. (*d*) Masson, J. C., and Mueller, S. C.: Surg., Gynec. & Obst. **56**:931, 1933. (*e*) Emge, L. A.: Am. J. Obst. & Gynec. **40**:738, 1940. (*f*) Shapiro, P. F.: Ann. Surg. **92**:1031, 1930. (*g*) Sailer, S.: Am. J. Clin. Path. **13**:271, 1943. (*h*) Cantor, P. J., and Kogut, B.: Am. J. Cancer **28**:760, 1936. (*i*) King, E. S. J., and Norris, J. H.: J. Coll. Surg. Australasia **3**:373, 1931.

5. Dionisi, H., and Ferraris, L. V.: Bol. y trab., Soc. de cir. de Córdoba **5**:179, 1944.

REPORT OF CASES

CASE 1.—Mrs. H. M., a 37 year old white woman, was admitted to the Presbyterian Hospital, service of Dr. N. C. Ochsenshirt, Feb. 23, 1945. She complained of irregular and prolonged menstrual periods of two years' duration, associated with mild weakness and fatigue. She was admitted because of a mass

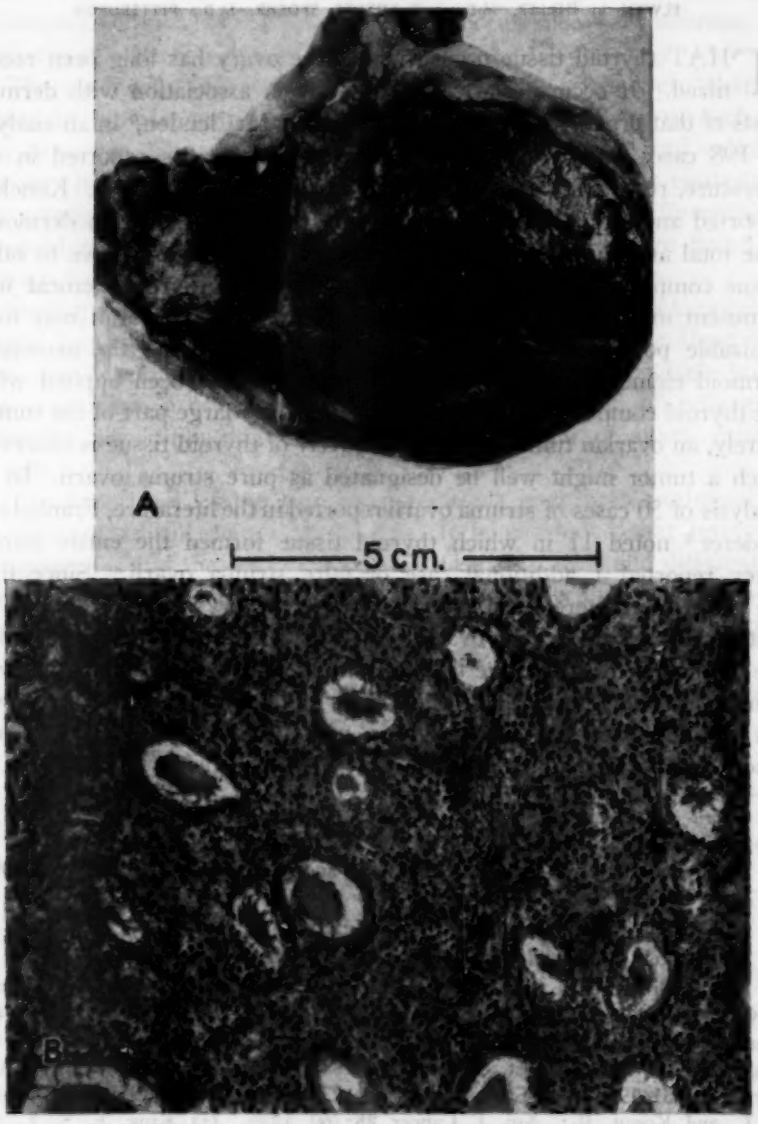

Fig. 1 (case 1).—*A*, struma ovarii surrounded by an ovarian capsule. Atrophic ovarian parenchyma appears to the left. The fimbriated extremity of the fallopian tube is above. The photograph illustrates the glistening fleshy cut surface of the tumor. *B*, typical thyroid tissue composed of large and small follicles; × 130.

in the pelvis, noted in the course of a premarital examination. There were no additional complaints and no evidence of hyperthyroidism.

Examination revealed nothing other than a firm, freely movable, nontender mass the size of an orange to the left of, and apparently attached to, the uterus, palpable only on bimanual pelvic examination. Laboratory examinations yielded normal results. The clinical impression was that of uterine fibroid, for which laparotomy was performed.

Approximately 2 liters of clear serous fluid was present in the peritoneal cavity. The mass noted on pelvic examination occupied the left ovary, which was removed along with a subserous adenomyoma 3 cm. in diameter attached to the anterior surface of the uterus. The peritoneum, the liver and other visible abdominal viscera were grossly normal.

After an uneventful convalescence, the patient was discharged on the twelfth postoperative day.

Pathologic Examination.—The ovary had been largely replaced by a solid ovoid tumor, 8 cm. in diameter, covered by an intact pale opaque ovarian capsule. On section, only atrophic remnants of ovarian parenchyma and an overdistended capsule enclosed the tumor (fig. 1*A*). The tumor tissue bulged slightly, was reddish brown, gelatinous, glistening and translucent. Numerous irregular opaque cellular-appearing areas were scattered throughout, their borders merging imperceptibly with the gelatinous matrix. Throughout the tumor were various-sized cysts containing colloid. Careful gross examination of closely spaced serial sections revealed no apparent variation in structure or appearance.

Microscopic Examination.—Several sections were made, and they all revealed thyroid tissue composed of follicles of fetal and adult type, the former predominating (fig. 1*B*). Solid columns, alveolar masses and small follicles containing little or no colloid bore striking resemblance to the so-called fetal adenoma of the thyroid gland. Scattered throughout were larger follicles with low columnar epithelium, appearing moderately hyperplastic. The enclosed colloid was acidophilic, and its edges were vacuolated and scalloped. Larger follicles contained more abundant colloid and were lined with cuboidal epithelium. The fibrous stroma was loose, edematous and in areas hemorrhagic. A loose edematous fibrous capsule separated the thyroid tissue from the surrounding ovarian cortex. Tissue other than thyroid was not demonstrable in the tumor.

To illustrate the much more common association of thyroid tissue with dermoid elements in struma ovarii we present a second case:

Case 2.—Mrs. F. W., a 60 year old white woman, was admitted to the Woman's Hospital, service of Dr. E. M. Baker, Aug. 1, 1945, complaining of vaginal discharge and urinary incontinence, present intermittently since parturition twenty-five years previously. Examination revealed advanced inflammatory disease and prolapse of the cervix and an old laceration of the urethral sphincter. A large cyst occupied the position of the left ovary, which was freely movable and not tender.

General examination revealed nothing noteworthy. The thyroid gland was not enlarged. There were no signs or symptoms of hyperthyroidism. Laboratory and roentgen studies disclosed nothing of note. On August 6 a vaginal and urethral plastic operation was performed. One week later left salpingo-oophorectomy and appendectomy were done. The postoperative course was uneventful.

Pathologic Examination.—The ovary was enlarged and ovoid, measuring 10 cm. in its greatest diameter. It had a fluctuant consistency and was covered by a pale, opaque, smooth, intact capsule. The fallopian tube, attached to the ovarian

capsule, was grossly normal except for flattening and elongation, the result of pressure. Several small subcapsular cysts containing clear watery fluid caused slight nodulation of the ovarian mass. On section a large unilocular cystic cavity was exposed, distended with yellowish brown amorphous granular caseous material containing numerous hair shafts. The cyst and its contents formed the bulk of the mass. The cyst wall, for the most part, was thin and leathery, averaging 2 mm. in thickness. Its inner lining was wrinkled and opaque, resembling epidermis, and from its surface numerous hair shafts extended into the cavity of the cyst. No dermoid papilla was evident. At one pole there was a prominent thickening of the cyst wall, the result of the presence of a sharply circumscribed oval lobular solid mass measuring 6 cm. in its greatest diameter (fig. 2). Its cut surface was reddish brown and studded with minute colloid vesicles typically thyroid in appearance. Following evacuation of the cyst contents, the nodular mass of thyroid tissue formed an estimated 75 per cent of the total bulk of the specimen.

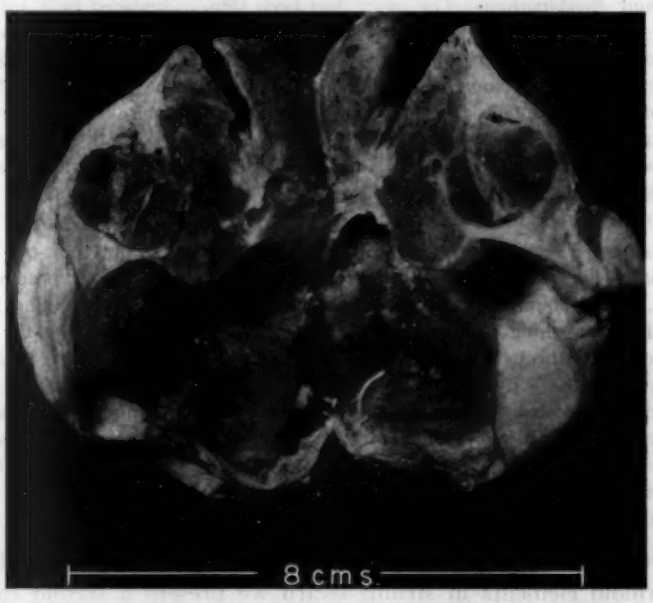

Fig. 2 (case 2).—Struma ovarii with dermoid cyst. The specimen has been hemisected and the cyst contents removed. The transected mass of thyroid tissue appears in the upper half of the object.

Microscopic Examination.—Sections revealed a thin, atrophic zone of ovarian cortex beneath a thin capsule. The bulk of the tissue was thyroid, composed of follicles which varied considerably in size. The majority were small, of the fetal type, and contained little or no colloid. The follicular epithelium was cuboidal in type. Other follicles were larger and contained normal amounts of old colloid. Still others formed small cysts, which were distended with colloid and lined by flattened epithelial cells. Infrequently the follicular epithelium assumed columnar characteristics, but the general picture was not that of hyperplasia. Areas of the stroma showed serous degeneration and small interstitial hemorrhages. A thin fibrous capsule separated the thyroid tissue from the surrounding ovarian parenchyma.

The cavity of the large central cyst was lined with stratified squamous epithelium, the outermost layers of which were cornifying and desquamating into the cavity of the cyst.

COMMENT

Although there was microscopic evidence of epithelial hyperplasia in case 1 and a large mass of ectopic thyroid tissue in both cases, the patients gave no clinical evidence of hyperthyroidism, and it must be assumed that the tissue was not physiologically overactive. Cases in which struma ovarii was associated with hyperthyroidism have been observed,[6] and reports of cancerous ovarian thyroid appear in the literature.[7]

Although several earlier investigators have questioned whether the tissue in such cases is truly thyroid, the overwhelming consensus of the present day accepts such an interpretation. The position was considerably strengthened by the work of Plaut,[8] who studied the pharmacologic and biologic activity of tissue from specimens of struma ovarii.

Thyroid tissue present in the ovary is generally regarded as a manifestation of teratomatous growth arising from totipotential germinal cells. The fact that other tissue elements occur in the ovary in the majority of cases lends support to such a concept. Not infrequently, one-sided overgrowth of the thyroid component renders the teratomatous nature inconspicuous, and unless the examination is most diligent and supported by numerous microscopic sections, other tissue components may be overlooked. It appears to be well established that pure struma, composed of thyroid tissue only, does occur, although rarely. In such cases the possibility of pressure atrophy, absorption and disappearance of other tissue elements must be conceded. The explanation of the selective overgrowth of thyroid tissue in a teratomatous ovarian neoplasm remains obscure.

SUMMARY

Two cases of struma ovarii have been observed, in one of which the tumor was composed entirely of thyroid tissue. It is probable that struma ovarii of the latter type is originally teratomatous and that the overgrowth of thyroid tissue ultimately destroys other tissue elements.

NOTE.—Following completion of this paper, several additional sections were made for teaching purposes from blocks of tissue in case 1. At one area within the ovarian thyroid there was a small acinus lined with columnar mucus-secreting epithelium, distinctly not thyroid in type. Although this nullifies the "pure" aspect of the struma, it supports the concept that struma ovarii is originally teratomatous.

6. (*a*) Moench, G. L.: Surg., Gynec. & Obst. **49**:150, 1929. (*b*) Emge.[4e] (*c*) Gusberg, S. B., and Danforth, D. N.: Am. J. Obst. & Gynec. **48**:537, 1944.

7. Wynne and others.[1] Emge.[4e] Shapiro.[4f]

8. Plaut, A.: Am. J. Obst. & Gynec. **25**:351, 1933.

HEPATIC ABSCESS COMPLICATING ATRESIA OF THE SMALL INTESTINE OF A NEWBORN INFANT

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HEPATIC abscess is comparatively rare in children and to encounter a well established abscess in a newborn infant is uncommon indeed. No instance of abscess of the liver of a newborn infant was found reported, but a report of abscess of the liver occurring at 6 weeks was found.[1]

The following report concerns a newborn infant with a hepatic abscess present at birth, who lived for thirty-nine hours.

REPORT OF A CASE

The mother, a patient of Dr. Edes Alsup, is Japanese, "aged 32, gravid five times, with four normal living female children." Althogh she had had nausea in early pregnancy, with vomiting on a few occasions, the course of pregnancy had been normal except for swelling of the ankles and "spilling of small amounts of water" for one week prior to admission.

On admission the mother showed slight edema of the ankles; the blood pressure was 140 systolic and 90 diastolic; she was "fully dilated" and in labor. The membranes were ruptured artificially, and the second stage was completed in about twenty-one minutes after admission. No gross abnormalities were observed in the placenta. She was discharged on the fifth day. Her blood showed: red cells, 4,970,000; hemoglobin content, 13.8 Gm.; white cells, 6,800, with 39 per cent polymorphonuclear leukocytes, 58 per cent lymphocytes and 3 per cent eosinophils. The feces revealed no parasites.

The baby was a girl, born in fair condition, who cried spontaneously. The whole body was described as hard and nonpitting, with an edematous appearance. The color became cyanotic, respiration was somewhat difficult, but oxygen improved the color. However, respiration remained grunty. After four hours, the swelling of the face and the hands was relieved somewhat, but the abdomen and the lower extremities remained edematous. Later, the edema improved further, urine was discharged in small amounts, vomiting of small amounts of bright green fluid followed and terminally there was a macular rash over the entire body, especially over the lower extremities and the abdomen. The cyanosis increased, the patient failed to respond to oxygen therapy and artificial respiration, and death occurred about thirty-nine hours after birth.

The infant's blood showed: erythrocytes, 5,710,000 per cubic millimeter; hemoglobin content, 16.5 Gm.; leukocytes, 20,500 per cubic millimeter, with 44 normoblasts per hundred cells in the differential count. A corrected estimate of the leukocyte count would be approximately 12,000 per cubic millimeter. The differential count showed polymorphonuclears 51 per cent, lymphocytes 38 per cent, eosinophils 4 per cent, monocytes 3 per cent and myelocytes 4 per cent. The erythrocyte count showed many microcytes and a few macrocytes with some

From the Department of Laboratories, Queens Hospital.

1. Kutsunai, T.: Am. J. Dis. Child. **51**:1385, 1936.

polychromasia. The infant's blood type was A and was Rh positive. (The mother's blood was of type AB and Rh positive.)

The blood nonprotein nitrogen of the baby was 31 mg. per hundred cubic centimeters; the blood sodium chloride, 499 mg., with 260 mg. as chlorine. The van den Bergh reaction showed 3 units, and the Weltmann coagulation band, 6.

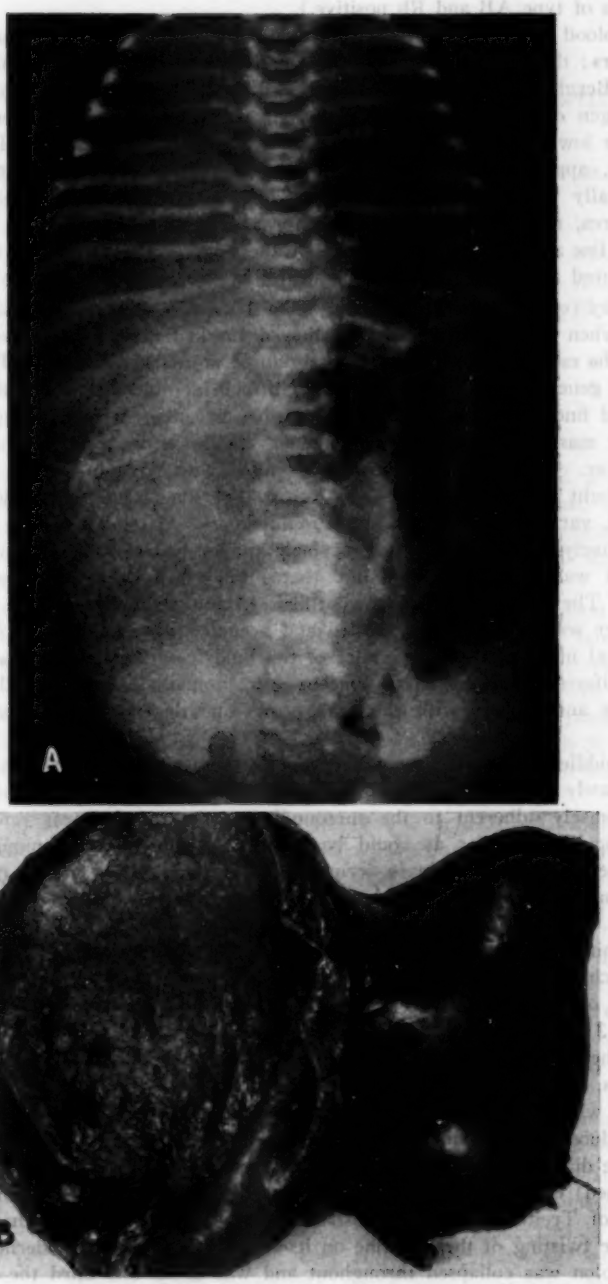
Roentgen examination showed three large masses in the abdomen: One lay under the lower seven ribs on the right side; another extended well down into the flank, apparently under the one just mentioned and down into the pelvis and laterally beyond the midline to the left; a third mass occupied the entire lumbar area, reaching over to the left for a distance of about 1 cm. beyond the vertebral line and apparently lying outside the pelvis. The left side of the abdomen was obscured and filled with gaseous shadows. No interpretation was given.

Autopsy (eight hours after death).—The brain was edematous. The lungs sank quickly when placed in water and showed marked atelectasis. The heart, the thymus, the esophagus and the thyroid disclosed no marked changes. The abdomen presented generalized plastic peritonitis with considerable matting of the intestines because of fine adhesions. The liver was densely adherent to the diaphragm, and the upper mass observed in the roentgenogram lay entirely within the right lobe of the liver. This mass was an abscess filled with dark brownish, cloudy fluid with a slight greenish tinge. The "capsule" of the abscess was thick and well developed, varying from 1 to 2 mm. in thickness. After evacuation the interior was relatively smooth except for a small amount of brownish granular deposit. The fluid was of a foul odor like that produced by the action of the colon bacillus. The abscess involved two thirds of the right lobe of the liver. The gallbladder was small and contracted and occupied its usual bed. The bile duct was normal in its relations. Culture of the fluid from the hepatic abscess showed many coliform organisms. No amebas were found. Microscopically, the wall was dense and fibrotic with calcific deposits and degeneration products of long standing.

The middle mass in the roentgenogram was a peritonealized abscess containing approximately 2 ounces (60 cc.) of fluid similar to that in the hepatic abscess. It was densely adherent to the surrounding structures and was separated with some difficulty. So far as could be determined, it did not communicate with any of the viscera. This mass occupied the greater portion of the right side of the abdomen, lying beneath and attached to the liver, and descending into the pelvis.

The third mass was a bulbous dilatation of a blind pouch above the midbowel area, which contained a foul-smelling, thin, brownish fluid of colon bacillus odor. Stretched over this mass was a threadlike atretic portion of the intestine, which extended 3 cm. beyond the margins of the mass. Above the bulbous dilatation was another elongated sacculation on one side. Beyond the atretic portion the ileum was collapsed and empty except for a large Meckel's diverticulum (2 by 0.75 cm.) which was found about 4 cm. below the obliterated area. The jejunum and the duodenum, on the other hand, except for the bulbous dilatation, were of average diameter and contained a moderate amount of liquid of yellowish brown (bile-stained) color and about ten soft pellet-like masses of greenish mucus. The ligament of Treitz acted as an obstructive band, with the result that there was a complete twisting of the intestine on itself with a loop lying underneath it.

The colon was collapsed throughout and was about one third the diameter of the small intestine. There was no evidence of meconium in the colon. The stomach was normal. The generalized peritonitis and adhesions have been mentioned.



A, roentgenogram showing an intrahepatic abscess, a subhepatic abscess and a bulbous dilatation of the small intestine above the atretic portion. *B*, upper surface of the liver showing a collapsed abscess.

The spleen, the kidneys, the adrenal glands, the fallopian tubes and the ovaries presented no gross abnormalities.

The diagnoses were: generalized peritonitis with adhesions; large hepatic abscess of the right lobe of long standing; right subhepatic peritonealized abscess; atresia of the jejunum with bulbous dilatation; Meckel's diverticulum; pulmonary atelectasis.

The gaseous shadows shown in the roentgenogram apparently did not arise from intestinal ballooning but from peritoneal pockets of gas produced by bacterial action. Figure *B* shows in the liver of the newborn infant a well defined abscess possessed of a definite "fibrous capsule" containing calcific deposits. The atresia of the jejunum had not led to as much general dilatation as might have been anticipated from a blind pouch deformity, but this was probably because the baby had not been fed anything beyond a small amount of water. The atresia probably played a prominent role in the production of intestinal obstruction in prenatal life, with probably a focus of healed perforation, followed by a hepatic and a peritonealized abscess. That the bulbous dilatation represented another dilated diverticulum is a possibility. There had apparently been reactivation of the peritonitis as a terminal event.

SUMMARY

A newborn infant with atresia of the small intestine had, in addition, a subhepatic abscess and a large abscess of the liver with calcific deposits in the fibrous wall.

Notes and News

Appointments.—Colonel Ashley W. Oughterson, of the Army Institute of Pathology, Washington, D. C., recently medical aide to General Douglas MacArthur and formerly clinical professor of surgery at Yale University, is now executive vice president of the American Cancer Society.

F. R. Dieuaide, formerly clinical professor of medicine at Harvard Medical School, has assumed the directorship of the Life Insurance Medical Research Fund. The purpose of this fund is to make grants to universities and medical schools for research on diseases of the heart and related conditions.

D. Murray Angevine, formerly a member of the department of pathology in Cornell University, has assumed the professorship of pathology in the University of Wisconsin, succeeding Charles H. Bunting, retired.

Brigadier General R. A. Kelser, of the United States Army, is retiring from active duty to become dean and professor of bacteriology of the College of Veterinary Medicine of the University of Pennsylvania. General Kelser has served for nearly eight years as director of the veterinary division of the Surgeon General's Office.

Eugene Hildebrand Jr., formerly of the department of pathology of Passavant Hospital, Chicago, is now pathologist and director of laboratories of the Great Falls Clinic, Great Falls, Mont.

S. E. Gould, pathologist to the Wayne County general hospital, Eloise, Mich., is now the editor of the *American Journal of Clinical Pathology*, succeeding I. Davidsohn, resigned.

Edith Sproul, New York, recently has been appointed to a professorship in pathology at the American University, Beirut, Lebanon.

Society News.—The American College of Surgeons will hold its thirty-second clinical congress at the Waldorf-Astoria Hotel, New York, Sept. 9 to 13, 1946.

The American Association for the Study of Goiter will hold its annual meeting at the Drake Hotel, Chicago, June 20 to 22.

At the meeting of the American Association of Pathologists and Bacteriologists in Chicago, March 8 and 9, W. D. Forbus was elected president, M. H. Soule vice president, H. T. Karsner secretary and A. R. Moritz treasurer. At its next annual meeting the association will be the guest of the Jefferson Medical College, Philadelphia, on the Friday and Saturday preceding the meetings of the Federation of American Societies for Experimental Biology. At this meeting a symposium will be conducted on "Necrotizing Hepatic Injury and Sequels," with Lieutenant Colonel Balduin Lucké as referee.

Fellowships in Public Health.—Physicians interested in training for full time public health positions should write to the State Department of Health, Albany 1, N. Y.

Hall of Fame.—The late Major Walter Reed (1851-1902), the chairman of the United States Army Commission which in 1900 by experiments demonstrated that yellow fever is caused by a filtrable virus and is transmissible to man by the mosquito Aedes aegypti, has been elected to the Hall of Fame of New York University.

Deaths.—Harold Eugene Robertson, professor of pathology at the University of Minnesota Graduate School and formerly head of the section on pathologic anatomy at the Mayo Clinic, died on March 8, aged 67.

Life Insurance Medical Research Fund.—One hundred and forty-six life insurance companies in the United States and Canada have cooperated to establish this fund in support of fundamental research bearing on cardiovascular disease, including rheumatic fever, hypertension, arteriosclerosis and allied disorders. To assist the directors of the fund in making grants, an advisory council has been appointed with the following membership: Francis G. Blake, chairman; Ernest W. Goodpasture, A. Baird Hastings, Eugene M. Landis, Robert F. Loeb, C. N. H. Long, Seeley G. Mudd and Cecil J. Watson. Grants will be made for periods according with the specific requirements of the research problems. Applications for grants may now be made and should be transmitted in duplicate through the administrative officer of the institution making application. Requests for grants should include a description of the proposed research, a budget, and the date when funds are desired. Applications received by Feb. 1, 1946 will be given consideration at a meeting of the council to be held on or about March 1, 1946. Address Francis G. Blake, Chairman, Advisory Council, 333 Cedar Street, New Haven 11, Conn.

Books Received

Kettle's Pathology of Tumors. By W. G. Barnard, F.R.C.P., professor of Pathology of the University of London and at St. Thomas's Hospital Medical School and director of pathology at St. Thomas's Hospital, London, and A. H. T. Robb-Smith, M.A. Oxon., M.D. London, Nuffield reader in pathology at the University of Oxford and director of pathology at Radcliffe Infirmary. Third edition. Pp. 318, with 191 illustrations. Price, $5.50. New York: Paul B. Hoeber, Inc., 1946.

First comes a section on the biology of tumors. Tumor is defined as an autonomous new growth which is "unlimited, progressive, purposeless, and uncontrolled." This description does not apply fully to all forms of benign, or noncancerous, neoplasms. The authors discuss clearly and instructively the general structure and growth of tumors, the differences between noncancerous and cancerous tumors ("innocency and malignancy"), the characteristics of cancer, its dissemination, its experimental induction and causes and the cancer theories. The general pathology of tumors is the subject of the second section. Comments on the nomenclature and on the histologic and embryologic classifications are followed by descriptions of the microscopic structure of tumors grouped as follows: innocent connective tissue tumors; sarcoma; innocent epithelial tumors (papilloma and adenoma); carcinoma; tumors of the nervous system; melanoma; endothelioma; teratoma. The third part deals summarily with the special features of tumors as they occur in various tissues and organs. The few lines about carcinoma of the larynx (pages 226 and 227) do not reflect the progress in its treatment since 1936, which is the date of the article to which readers are referred for an analysis of the results of its treatment. The point of origin in most cases is a true vocal cord and not the piriform sinus. On page 233 one reads: "Ahlbom has suggested that pharyngeal carcinoma in women only occurs in those suffering from chronic hypochromic anaemia with atrophy of the mucous membrane." "Only" should be "mostly" or some word of like meaning. Most of the illustrations are microscopic drawings by Kettle himself "to show clearly the points described," but at this time and place they look strange—well made, it is true, but unreal and idealized. There are many unfamiliar words, especially in the discussions of classifications. The writing would have been simpler if the word cancer had been used in place of "malignant tumor," "malignancy," "malignant neoplastic disease." "Cancer" is now used to designate cancerous neoplasms so generally in common parlance, in names and in popular and nonmedical, as well as scientific, literature that there should be no hesitancy any longer to use it in textbooks wherever its use is indicated. On the whole, the book continues to be an excellent introduction to the study of tumors, better suited perhaps, on account of its terminology, for British than for American medical students.